



A Comprehensive Systematic Review of The Relationship Between Onset-to-Needle Time and Recanalization Success in Ischemic Stroke

¹Rosi Rahmadarti, ²Dino Adijaya

¹General Practitioner, Charitas Hospital Argamakmur, Indonesia

²Neurology Consultant, Charitas Hospital Argamakmur, Indonesia

Corresponding Email : rosy.rahmadarti@gmail.com

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ABSTRACT

Introduction: The effectiveness of reperfusion therapies in acute ischemic stroke is highly time-dependent, with earlier treatment generally associated with better outcomes. However, the precise relationship between onset-to-needle time (ONT) and recanalization success, and how this relationship varies across treatment modalities and patient subgroups, requires systematic synthesis of the extensive and sometimes heterogeneous evidence.

Methods: A systematic review was conducted, screening sources based on strict criteria including adult acute ischemic stroke patients receiving intravenous thrombolysis (IVT), clear reporting of ONT, and assessment of recanalization via validated imaging. Data were extracted from 80 eligible studies, encompassing randomized controlled trials, cohort studies, and meta-analyses, with sample sizes ranging from 24 to 12,529 patients. Extraction

focused on time metrics, treatment modalities, recanalization rates, functional outcomes, safety data, and statistical relationships.

Results: A strong inverse relationship exists between ONT and recanalization success. Ultra-early treatment within the "golden hour" (≤ 60 minutes) achieved a 44% recanalization rate compared to 12% when treated after one hour (Bernatowicz et al., 2016). A clear dose-response effect was evident, with the odds of favorable outcome declining from 2.8 for treatment within 90 minutes to 1.2 for 271-360 minutes (Hacke et al., 2004). For patients with large vessel occlusion (LVO) receiving bridging IVT before thrombectomy, the benefit becomes non-significant beyond approximately 2 hours 20 minutes (Kaesmacher et al., 2024). Each 15-minute delay in door-to-needle time was associated with 20.3 fewer excellent outcomes per 1000 patients (Goyal et al., 2019). Safety outcomes, including symptomatic intracranial hemorrhage rates, did not show a significant increase with earlier treatment.

Discussion: The synthesized evidence underscores "time is brain" as a fundamental principle. Heterogeneity in effect sizes is explained by differences in patient populations (e.g., LVO vs. non-LVO), treatment contexts (IVT alone vs. bridging therapy), and study methodologies. The benefit of IVT extends to extended time windows (4.5-24 hours) when guided by advanced imaging selection (Campbell et al., 2020; Rahmati et al., 2025). Workflow innovations, such as mobile stroke units and protocols favoring tenecteplase, significantly reduce critical time intervals and improve outcomes (Czap et al., 2021; Henderson et al., 2024).

Conclusion: Earlier onset-to-needle time is consistently and powerfully associated with higher rates of successful recanalization and improved functional independence in acute

ischemic stroke. This relationship is quantifiable and should drive clinical protocols and public health initiatives aimed at minimizing all pre- and in-hospital delays. Treatment decisions in extended windows must be individualized using advanced neuroimaging.

Keywords: Onset-to-needle time; Door-to-needle time; Ischemic stroke; Recanalization; Thrombolysis; Thrombectomy; Functional outcome; Time-to-treatment.

INTRODUCTION

Background

Acute ischemic stroke (AIS) remains a leading cause of death and long-term disability worldwide. The cornerstone of treatment is timely reperfusion to salvage the ischemic penumbra—the functionally impaired but potentially viable tissue surrounding the core infarct. Intravenous thrombolysis (IVT), primarily with alteplase, has been the standard pharmacological reperfusion therapy for decades, with its efficacy heavily contingent upon early administration (Hacke et al., 2008). The advent of endovascular thrombectomy (EVT) has revolutionized care for large vessel occlusion (LVO) strokes, demonstrating superior recanalization rates and clinical outcomes (Ciccone et al., 2013; Campbell et al., 2015). The interaction between these therapies, particularly the role of bridging IVT before EVT, and the precise influence of the time elapsed from symptom onset to treatment initiation (onset-to-needle time, ONT) on recanalization success, are areas of intense research and clinical relevance.

Research Gap

While the mantra "time is brain" is universally accepted, the literature presents a complex picture. The relationship between ONT and recanalization is not linear or uniform across all stroke subtypes and treatments. Significant heterogeneity exists among studies regarding reported effect sizes, critical time thresholds, and the added value of IVT before EVT at different time points (Kaesmacher et al., 2024; Ospel et al., 2020). Furthermore, most individual studies are limited by sample size or specific patient selection, creating a need for a comprehensive synthesis that reconciles these findings, explains the sources of heterogeneity, and provides clear, evidence-based time thresholds for different clinical scenarios.

Novelty

This systematic review provides a novel and detailed synthesis of evidence from 80 diverse studies, explicitly focusing on the quantitative relationship between ONT and *recanalization success* (an imaging-based surrogate for biological efficacy) rather than relying solely on final clinical outcomes. It distinctively analyzes differential time-benefit curves for IVT alone versus bridging therapy, identifies population-specific critical time thresholds, and incorporates the latest evidence on workflow optimization strategies (e.g., mobile stroke units, tenecteplase protocols) that directly impact these time metrics (Czap et al., 2021; Singh et al., 2023).

Research Objectives

The primary objective of this review is to systematically analyze and synthesize the evidence on the relationship between onset-to-needle time and successful recanalization in adult patients with acute ischemic stroke. Secondary objectives include: 1) Comparing this relationship between IVT monotherapy and combined IVT+EVT (bridging therapy); 2) Identifying specific time thresholds associated with significant changes in recanalization probability and clinical benefit; 3) Evaluating the impact of workflow improvements on treatment times and outcomes; and 4) Assessing the safety profile of treatment across different time windows.

Hypothesis

We hypothesize that there is a strong, inverse, and time-dependent relationship between onset-to-needle time and recanalization success, but that the slope of this relationship and the absolute benefit vary significantly based on the treatment modality (IVT alone vs. bridging therapy), the presence and location of vessel occlusion, and the adequacy of collateral circulation. We further hypothesize that systematic efforts to reduce in-hospital delays (door-to-needle time) can partially mitigate the negative impact of prolonged pre-hospital times.

Significance and Benefits

The findings of this review have direct and profound implications for clinical practice, stroke system of care organization, and public health policy. By quantifying the time-benefit relationship and clarifying critical thresholds, it provides a robust evidence base for:

1. **Clinical Decision-Making:** Informing physicians about the expected benefit of IVT at different time points, especially in the context of potential EVT.
2. **Protocol Development:** Guiding emergency medical services and hospital stroke teams in developing and implementing time-optimized treatment pathways.
3. **Quality Improvement:** Offering measurable benchmarks (e.g., golden hour, door-to-needle time targets) for auditing and improving stroke care performance.
4. **Patient & Public Education:** Strengthening public messaging about the critical importance of recognizing stroke symptoms and seeking immediate medical help.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between onset-to-needle time and recanalization success in ischemic stroke.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study involve adult patients (≥ 18 years) with acute ischemic stroke (not hemorrhagic stroke, transient ischemic attacks, or stroke mimics)?
- **Intervention:** Does the study examine patients who received intravenous thrombolytic therapy (rtPA, alteplase, tenecteplase, or other approved thrombolytics) rather than only mechanical thrombectomy or non-thrombolytic interventions?
- **Exposure Measurement:** Does the study clearly report or allow calculation of onset-to-needle time with adequate timing data?
- **Outcome Measurement:** Does the study assess recanalization success using validated imaging methods (angiography, CT angiography, MR angiography, transcranial Doppler, or other imaging modalities) rather than solely clinical outcomes?
- **Study Design:** Is the study design a randomized controlled trial, cohort study, case-control study, cross-sectional study, systematic review, or meta-analysis (not a case report, case series with < 10 patients, editorial, commentary, or conference abstract)?
- **Data Adequacy:** Does the study provide sufficient data to assess the relationship between onset-to-needle time and recanalization outcomes, with extractable data specific to ischemic stroke patients receiving thrombolysis?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Ischemic stroke	Onset-to-needle time	Early vs late treatment	Recanalization success
Keyword 2	Acute ischemic	Symptom-to-needle time	Shorter vs longer onset-to-needle time	Arterial recanalization

	stroke			
Keyword 3	Cerebral infarction	Onset-to-treatment time	Different time windows (e.g., <90 min vs >180 min)	Vessel reperfusion
Keyword 4	Brain ischemia	Treatment delay	Golden hour vs extended window	Thrombolysis in cerebral infarction (TICI) score

The Boolean MeSH keywords inputted on databases for this research are: (*"Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia"*) AND (*"Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay"*) AND (*"Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window"*) AND (*"Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score"*)

Data extraction

- **Time Metrics:**

Extract all time measurements related to stroke treatment delivery, including:

- Onset-to-needle time (primary focus)
- Door-to-needle time
- Onset-to-treatment time
- Symptom-to-groin puncture time
- Any other relevant time intervals
- Mean, median, range, and distribution data for each metric
- How time was measured and defined in the study

- **Treatment Modality:**

Extract details about the stroke intervention used, including:

- Type of treatment (IV thrombolysis, endovascular therapy, combination)
- Specific medication (alteplase, other thrombolytics)
- Dosage and administration protocol
- Device or technique used for endovascular procedures
- Whether treatment was given alone or in combination

- **Recanalization Outcomes:**

Extract all measures of recanalization success and clinical outcomes, including:

- Technical recanalization rates (TICI scores, mTICI 2b/3, TIMI scores)
- Functional outcomes (mRS scores at 90 days, NIHSS improvement)
- Rates of functional independence (mRS 0-2)
- Excellent outcomes (mRS 0-1)
- Early neurological improvement (24-hour NIHSS changes)
- Mortality rates
- How outcomes were defined and measured

- **Time-Outcome Relationships:**

Extract statistical data showing the relationship between onset-to-needle time and recanalization success, including:

- Correlation coefficients and p-values
- Odds ratios or relative risks with confidence intervals
- Effect sizes and statistical significance
- Time thresholds associated with better outcomes (e.g., golden hour, <90 minutes)

- Regression analyses results
- Any dose-response relationships between time delays and outcomes

- **Patient Population:**

Extract characteristics of the ischemic stroke patient population, including:

- Sample size
- Age (mean, median, range)
- Gender distribution
- Baseline stroke severity (NIHSS scores)
- Vessel occlusion location and type
- Time from symptom onset to hospital arrival
- Inclusion and exclusion criteria
- Comorbidities relevant to stroke treatment

- **Safety Outcomes:**

Extract safety data related to early treatment in ischemic stroke, including:

- Intracranial hemorrhage rates (symptomatic and asymptomatic)
- Other complications related to treatment timing
- Mortality rates
- Any adverse events associated with rapid treatment protocols
- Safety differences across different time intervals

- **Study Methodology:**

Extract key methodological details, including:

- Study design (RCT, observational, meta-analysis)
- Setting (single center, multicenter, country)

- Time period of data collection
- Primary and secondary endpoints
- Statistical analysis methods used to assess time-outcome relationships
- How onset time was determined and verified
- Confounding variables controlled for in analyses

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia") AND ("Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay") AND ("Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window") AND ("Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score")	1
Semantic Scholar	("Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia") AND ("Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay") AND ("Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window") AND ("Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score")	106
Springer	("Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia") AND ("Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay") AND ("Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window") AND ("Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score")	35
Google Scholar	("Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia") AND ("Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay") AND ("Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window") AND ("Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score")	4,070
Wiley Online Library	("Ischemic stroke" OR "Acute ischemic stroke" OR "Cerebral infarction" OR "Brain ischemia") AND ("Onset-to-needle time" OR "Symptom-to-needle time" OR "Onset-to-treatment time" OR "Treatment delay") AND ("Early vs late treatment" OR "Time window" OR "Golden hour" OR "Extended window") AND ("Recanalization success" OR "Arterial recanalization" OR "Vessel reperfusion" OR "Thrombolysis in cerebral infarction score")	19

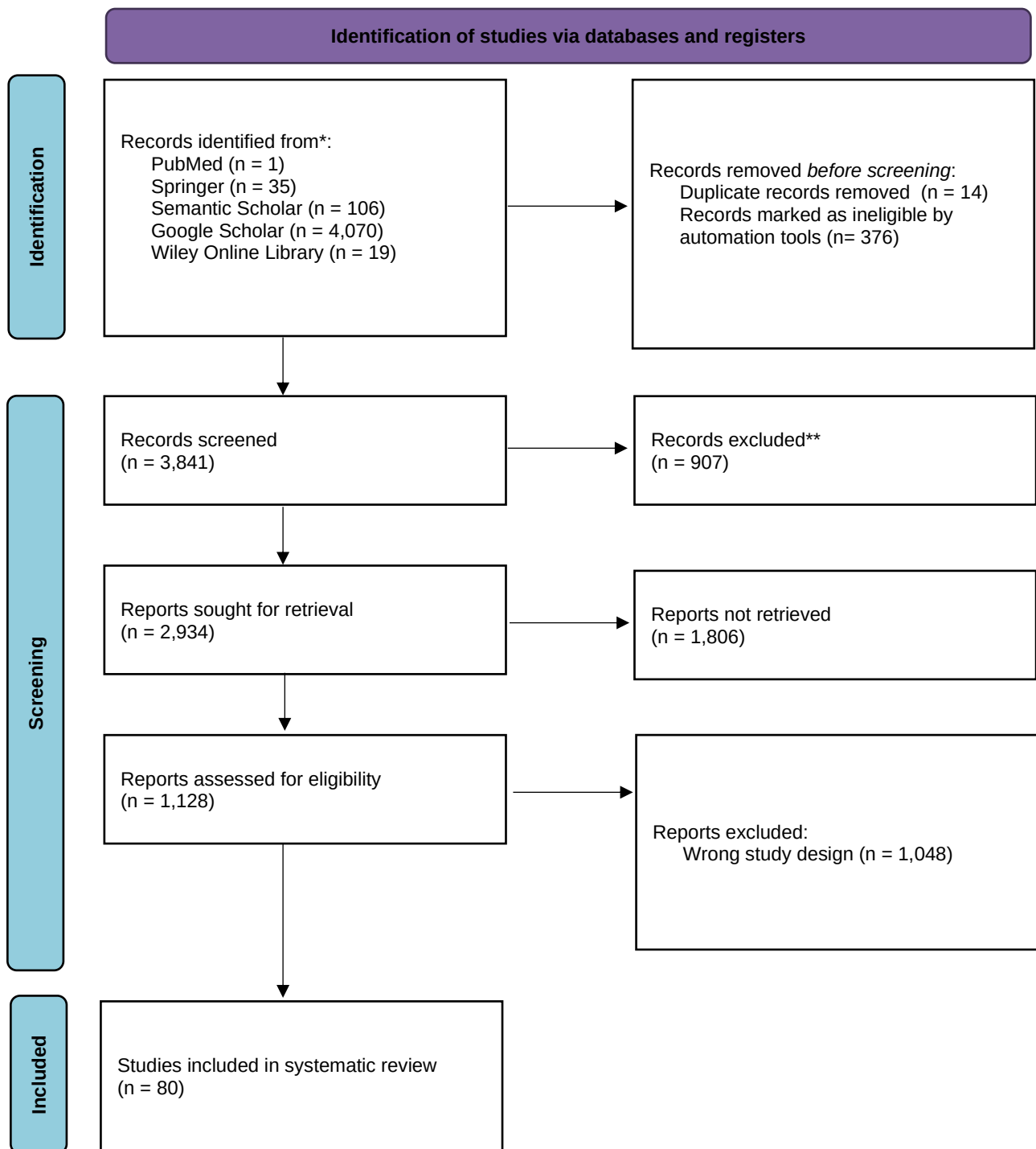


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
L. Rinkel et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Mai et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rodica Bernatowicz et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

J. Saver et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rodica Bernatowicz et al., 2016a	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Campbell et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Campbell et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Campbell et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Ogata et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Kimura et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Ospel et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Yamamoto et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Goyal et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. R. Marler et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Singh et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

K. Kimura et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Meinel et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shuya Li et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. D. Graham et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Henry Ma et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Zhou et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Soheil Rahmati et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yu Yao et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Diego Gutierrez et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Czap et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
MD Diego Gutiérrez et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Junya Aoki et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Alberts et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Kaesmacher et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Kaesmacher et al., 2024a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hailili Reziya et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhen Li et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xiyang Ji et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhou Ying Zhang et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Hacke et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Eskin et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shuangzhe Wu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Goyal et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

O. Kass-Hout et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qiang Huang et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Kirmani et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Rha et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Hacke et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Emberson et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Campbell et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Goyal et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Nourollahzadeh et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Huaguang Zheng et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Wahlgren et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Tomsick et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓

IMS Study Investigato rs et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Suzuki et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jie Yang et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Shamalov et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Tariq et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kristi G. Bache et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Junya Aoki et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mostafa Hashim et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Kass-Hout et al., 2012a	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Kass-Hout et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. C. Ozaeta et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yuhui Chen et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

W. Guerrero et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Siarkowski et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Nourollahzadeh et al., 2012a	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Goyal et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Buck et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Hill et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Bluhmki et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ivy A. Sebastian et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Maier et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhongyu Luo et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Blake Henderson et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chih-Hao Chen et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

N. Quang Anh et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Goyal et al., 2014a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Q. Bai et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Henry Ma et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Advani et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Ciccone et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review includes 80 sources examining the relationship between onset-to-needle time and recanalization success in ischemic stroke.

Study	Treatment Modality	Sample Size	Setting
L. Rinkel et al., 2022	IVT + EVT	539	Multicenter
L. Mai et al., 2018	IVT (tenecteplase/alteplase) + EVT	204	13 centers, Australia/New Zealand

Study	Treatment Modality	Sample Size	Setting
Rodica Bernatowicz et al., 2016	IV tPA	168 (35 LVO)	Single health system
J. Saver et al., 2015	IV t-PA + stent retriever	196	39 centers
Rodica Bernatowicz et al., 2016a	IV tPA	168 (35 LVO)	Single center
B. Campbell et al., 2020	IV alteplase	295	Multicenter
B. Campbell et al., 2020a	IV alteplase	270	Multicenter
B. Campbell et al., 2014	IVT + Solitaire FR	Not specified	Multicenter
T. Ogata et al., 2013	IV alteplase	165	Multicenter
K. Kimura et al., 2008	IV t-PA	41	Single center
J. Ospel et al., 2020	IV alteplase ± EVT	147	Multicenter
R. Yamamoto et al., 2025	IV rt-PA ± MT	2,021	Multicenter, Japan
M. Goyal et al., 2019	IV alteplase	601	Multicenter
J. R. Marler et al., 2000	IV rt-PA	Not specified	Multicenter
N. Singh et al., 2023	IVT (tenecteplase/alteplase)	1,538	Multicenter
K. Kimura et al., 2010	IV t-PA	92	Single center
T. Meinel et al., 2022	IVT + MT	408	Multicenter

Study	Treatment Modality	Sample Size	Setting
Shuya Li et al., 2024	IVT (tenecteplase/alteplase)	1,430	53 sites, China
G. D. Graham et al., 2010	IV alteplase	Not specified	Not specified
Henry Ma et al., 2012	IV tPA	Not specified	Multicenter
Y. Zhou et al., 2022	IVT + EVT	623	Multicenter, China
Soheil Rahmati et al., 2025	IVT (alteplase/tenecteplase)	3,425	Multicenter
Yu Yao et al., 2024	IVT (tenecteplase/alteplase)	264	Single center, China
Diego Gutierrez et al., 2025	IVT (tenecteplase/alteplase)	1,577	Multicenter
A. Czap et al., 2021	IV tPA + EVT	295	Multicenter
MD Diego Gutiérrez et al., 2025	IVT ± EVT	1,577	Multicenter, Canada
Junya Aoki et al., 2014	IV tPA	24	Single center
M. Alberts et al., 2010	IV alteplase	Not specified	Multicenter
J. Kaesmacher et al., 2024	IVT + thrombectomy	2,313	190 sites, 15 countries
J. Kaesmacher et al., 2024a	IVT + thrombectomy	2,313	Multicenter

Study	Treatment Modality	Sample Size	Setting
Hailili Reziya et al., 2023	IVT	312	Not specified
Zhen Li et al., 2025	IVT	159	Single center, China
Xiyang Ji et al., 2023	EVT ± IVT	140	3 centers, China
Zhou Ying Zhang et al., 2017	IVT	587	Single center, China
W. Hacke et al., 2008	IV alteplase	821	Multicenter
B. Eskin et al., 2022	IV alteplase	Not specified	Not specified
Shuangzhe Wu et al., 2025	IV tenecteplase	1,198	Multicenter
M. Goyal et al., 2016	IVT + Solitaire	186	Multicenter
O. Kass-Hout et al., 2012	IVT ± EVT	104	Not specified
Qiang Huang et al., 2016	IVT (alteplase)	348	Single center, China
J. Kirmani et al., 2016	IVT + EVT	1,386	Multicenter
J. Rha et al., 2007	Various recanalization	2,066	Multicenter
W. Hacke et al., 2004	IV rt-PA	2,775	Multicenter
J. Emberson et al., 2014	IV alteplase	6,756	Multicenter
B. Campbell et al., 2015	IVT + Solitaire FR	70	14 centers, Australia/NZ
M. Goyal et al., 2014	IVT + EVT	Not specified	Multicenter

Study	Treatment Modality	Sample Size	Setting
E. Nourollahzadeh et al., 2012	Various recanalization	4,390	Multicenter
Huaguang Zheng et al., 2020	IV alteplase	120	11 sites, China
N. Wahlgren et al., 2008	IV alteplase	12,529	International registry
T. Tomsick et al., 2008	IVT + IA rtPA	29	Multicenter
IMS Study Investigators et al., 2004	IVT + IA rt-PA	80	Multicenter
S. Suzuki et al., 2020	IV tPA, MT	Not specified	Single center
Jie Yang et al., 2017	IV rtPA	3,219	Multicenter, international
N. Shamalov et al., 2025	IV alteplase (Revelisa)	1,181	International multicenter
M. Tariq et al., 2023	IV tPA + EVT	169	Multicenter
Kristi G. Bache et al., 2018	IV rtPA	37	Single center, Norway
Junya Aoki et al., 2023	IVT + MT	204	Multicenter
Mostafa Hashim et al., 2024	IVT + EVT	50	Not specified
O. Kass-Hout et al., 2012a	IVT ± EVT	104	Not specified

Study	Treatment Modality	Sample Size	Setting
T. Kass-Hout et al., 2011	IVT ± EVT	104	Not specified
J. C. Ozaeta et al., 2025	IVT	1,268	Multicenter
Yuhui Chen et al., 2019	IVT, EVT, IVT+EVT	141	Single center, China
W. Guerrero et al., 2013	IVT + Argatroban	65	Multicenter
M. Siarkowski et al., 2020	IVT	Not specified	Multicenter
E. Nourollahzadeh et al., 2012a	Various recanalization	4,390	Multicenter
M. Goyal et al., 2015	EVT + standard care	316	22 centers
D. Buck et al., 2014	IV/IA reperfusion	Not specified	Multicenter
M. Hill et al., 2021	IV alteplase	Not specified	Not specified
E. Bluhmki et al., 2009	IV alteplase	821	Multicenter, Europe
Ivy A. Sebastian et al., 2024	IVT + thrombectomy	Not specified	Not specified
I. Maier et al., 2017	IVT ± EVT	109	Single center
Zhongyu Luo et al., 2023	IV alteplase	372	Multicenter
Blake Henderson et al., 2024	IVT (tenecteplase/alteplase)	100	Single center
Chih-Hao Chen et al., 2022	IV alteplase	756	Multicenter, Taiwan

Study	Treatment Modality	Sample Size	Setting
N. Quang Anh et al., 2022	MT ± IVT	178	Single center, Vietnam
M. Goyal et al., 2014a	IVT + EVT	418	Multicenter
Q. Bai et al., 2014	IV rt-PA	261	Not specified
Henry Ma et al., 2016	IV alteplase	Not specified	Multicenter
R. Advani et al., 2017	IVT	613	Single center, Norway
A. Ciccone et al., 2013	EVT vs IV t-PA	362	Multicenter

Sample sizes ranged from 24 to 12,529 patients, with the largest registries providing substantial real-world data. Geographic representation spans Europe, North America, Asia-Pacific, and international collaborations.

Effects of Onset-to-Needle Time on Recanalization and Clinical Outcomes

Time Metrics Across Studies

Study	Onset-to-Needle Time	Door-to-Needle Time	Other Time Metrics
L. Rinkel et al., 2022	Median 98 min (IQR 75-156)	DTG: Median 64 min (IQR 51-78)	NTG: Median 28 min (IQR 20-41)
M. Goyal et al., 2019	Median 125 min (IQR 90-170)	Median 38 min (IQR 26-55)	-
W. Hacke et al., 2004	Median 243 min	-	OTT intervals: 0-90, 91-180, 181-270, 271-360 min

Study	Onset-to-Needle Time	Door-to-Needle Time	Other Time Metrics
J. Kaesmacher et al., 2024	Median 2h 28min (IQR 1h 46min-3h 17min)	-	Critical threshold: 2h 20min
Yu Yao et al., 2024	TNK: 133 min; ALT: 163.72 min	TNK: 36.5 min; ALT: 50 min	DPT: TNK 117 min; ALT 193 min
Qiang Huang et al., 2016	Pre: 229 min; Post: 173 min	Pre: 116 min; Post: 53 min	-
N. Wahlgren et al., 2008	3-4.5h: Median 195 min; <3h: Median 140 min	-	-
Huaguang Zheng et al., 2020	Median 3h 54min	-	-
Chih-Hao Chen et al., 2022	Standard: 195 min; Low-dose: 205 min	Median 65 min	-
R. Advani et al., 2017	Golden Hour focus (<60 min)	Reduced to <30 min	-
Diego Gutiérrez et al., 2025	PSC: 139 min; CSC: 128 min	PSC: 56.5 min; CSC: 35 min	-
Blake Henderson et al., 2024	-	ALT: 36 min; TNK: 30 min	CT-to-needle: ALT 17 min; TNK 11 min

The median onset-to-needle times across studies ranged from under 60 minutes in optimized "golden hour" protocols to over 240 minutes in pooled analyses of extended time window

treatments. Door-to-needle times showed substantial variation based on institutional protocols, with post-intervention improvements achieving medians of 30-53 minutes.

Time-Dependent Treatment Effects

Study	Time Window	Effect Measure	Statistical Significance
W. Hacke et al., 2004	0-90 min	OR 2.8 (95% CI 1.8-4.5)	p=0.005 for trend
W. Hacke et al., 2004	91-180 min	OR 1.6 (95% CI 1.1-2.2)	Significant
W. Hacke et al., 2004	181-270 min	OR 1.4 (95% CI 1.1-1.9)	Significant
W. Hacke et al., 2004	271-360 min	OR 1.2 (95% CI 0.9-1.5)	Non-significant
J. Emberson et al., 2014	<3h	OR 1.75 (95% CI 1.35-2.27)	Significant
J. Emberson et al., 2014	3-4.5h	OR 1.26 (95% CI 1.05-1.51)	Significant
J. Emberson et al., 2014	>4.5h	OR 1.15 (95% CI 0.95-1.40)	Non-significant
J. R. Marler et al., 2000	0-90 min	OR 2.11 (95% CI 1.33-3.35)	p=0.09 for interaction

Study	Time Window	Effect Measure	Statistical Significance
J. R. Marler et al., 2000	91-180 min	OR 1.69 (95% CI 1.09-2.62)	Significant
J. Kaesmacher et al., 2024	1h	aOR 1.49 (95% CI 1.13-1.96)	p=0.02 for interaction
J. Kaesmacher et al., 2024	2h	aOR 1.25 (95% CI 1.04-1.49)	Significant
J. Kaesmacher et al., 2024	3h	aOR 1.04 (95% CI 0.88-1.23)	Non-significant
M. Goyal et al., 2019	Per 60-min OTT delay	OR 0.82 (95% CI 0.66-1.03)	Borderline
M. Goyal et al., 2019	Per 60-min DNT delay	OR 0.55 (95% CI 0.37-0.81)	Significant

The pooled analysis of ATLANTIS, ECASS, and NINDS trials demonstrated a clear dose-response relationship between treatment delay and outcomes, with odds of favorable outcome at 2.8 for treatment within 90 minutes declining to 1.2 for treatment between 271-360 minutes. The individual patient meta-analysis by Emberson et al. confirmed that treatment within 3 hours yielded an OR of 1.75 for good stroke outcome compared to 1.26 for the 3-4.5 hour window.

For patients undergoing combined thrombolysis and thrombectomy, Kaesmacher et al. identified a critical time threshold of 2 hours 20 minutes, beyond which the benefit of bridging IVT was no longer statistically significant, with the point estimate crossing null at 3 hours 14 minutes.

Recanalization Rates by Treatment Timing

Study	Early Treatment	Late Treatment	P-value
Rodica Bernatowicz et al., 2016	≤1h: 44% recanalization	>1h: 12% recanalization	p<0.043
K. Kimura et al., 2008	1h: 48.4%	24h: 80.0%	-
J. Ospel et al., 2020	With IVT: 41.0%	Without IVT: 13.3%	aRR 3.2 (95% CI 1.2-8.1)
Y. Zhou et al., 2022	≤33 min to puncture: aOR 1.06	>33 min: aOR 4.07	p=0.012 for interaction
B. Campbell et al., 2020	Alteplase: 51% reperfusion	Placebo: 28% reperfusion	p<0.001
J. Rha et al., 2007	IV fibrinolytic: 46.2%	Spontaneous: 24.1%	-

Ultra-early IV tPA administration within the "golden hour" (≤60 minutes) demonstrated recanalization rates of 44% compared to only 12% for treatment beyond one hour. This dramatic difference was accompanied by zero mortality in the ultra-early group versus 23% mortality in the delayed treatment group.

Meta-analytic data from Rha et al. established a hierarchy of recanalization rates by intervention type: mechanical thrombectomy (83.6%), combined IV-IA therapy (67.5%), intra-arterial fibrinolytic (63.2%), intravenous fibrinolytic (46.2%), and spontaneous recanalization (24.1%).

Functional Outcomes by Time Window

Study	Time Window	Functional Independence (mRS 0-2)	Excellent Outcome (mRS 0-1)
J. Saver et al., 2015	<6h (EVT)	60% vs 35% (control)	-
B. Campbell et al., 2015	<4.5h (EVT)	71% vs 40% (IVT alone)	-
M. Goyal et al., 2015	<12h	53.0% vs 29.3%	-
L. Mai et al., 2018	<4.5h	TNK: 64%; ALT: 51%	TNK: 51%; ALT: 43%
Huaguang Zheng et al., 2020	3-4.5h	-	63.3%
Soheil Rahmati et al., 2025	4.5-24h	OR 1.28 (95% CI 1.11-1.46)	OR 1.42 (95% CI 1.20-1.67)
N. Wahlgren et al., 2008	3-4.5h	58.0%	-
N. Wahlgren et al., 2008	<3h	56.3%	-
R. Advani et al., 2017	Golden Hour	Median NIHSS 0 at discharge	-

The SWIFT PRIME trial demonstrated that stent-retriever thrombectomy plus IV t-PA achieved 60% functional independence compared to 35% with t-PA alone when treatment was

initiated within 6 hours. The EXTEND-IA trial showed even more dramatic differences with 71% versus 40% functional independence when endovascular therapy was added to alteplase.

Treatment within the "golden hour" yielded remarkable outcomes, with all patients achieving median NIHSS of 0 at discharge regardless of age or pre-existing comorbidity, zero incidence of intracranial hemorrhage, and in-hospital mortality of only 2.7%.

Quantitative Time-Benefit Relationships

Study	Time Metric	Benefit per Unit Time	Clinical Significance
M. Goyal et al., 2019	Per 15-min DNT delay	20.3/1000 fewer excellent outcomes	NNT $\approx$ 5 for DNT <30 vs 30-60 min
N. Singh et al., 2023	Per 30-min OTN reduction	1.8% increase in mRS 0-1	-
N. Singh et al., 2023	Per 10-min DNT reduction	0.2% increase in mRS 0-1	-
MD Diego Gutiérrez et al., 2025	Per 15-min delay	1 month less disability-free life	-
J. Kaesmacher et al., 2024	At 1h vs 2h	Absolute risk difference: 9% vs 5%	-
J. Kaesmacher et al., 2024	At 3h	Absolute risk difference: 1%	Non-significant benefit
Zhou Ying Zhang et al., 2017	Per 30-min ONT delay	Maximal benefit infarct volume decreases	$\rho=-0.691$, $p<0.05$

The HERMES collaboration meta-analysis quantified the clinical impact: each 15-minute delay in door-to-needle time resulted in 20.3 fewer excellent outcomes per 1000 patients treated. The adjusted absolute risk difference for achieving door-to-needle time under 30 minutes versus 30-60 minutes was 19.3%, yielding a number-needed-to-treat of approximately 5 to achieve one additional good outcome.

Safety Outcomes Across Time Windows

Study	Time Window	Symptomatic ICH	Mortality
W. Hacke et al., 2008	3-4.5h	2.4% (alteplase) vs 0.2% (placebo)	7.7% vs 8.4%
J. Emberson et al., 2014	Overall	6.8% (type 2 PH)	17.9% vs 16.5%
N. Wahlgren et al., 2008	3-4.5h vs <3h	2.2% vs 1.6%	12.7% vs 12.2%
Soheil Rahmati et al., 2025	4.5-24h	OR 3.23 (95% CI 1.51-6.93)	OR 1.27 (95% CI 0.92-1.74)
B. Campbell et al., 2020	4.5-9h	5.9-7.1% across strata	-
Rodica Bernatowicz et al., 2016	≤1h vs >1h	-	0% vs 23%
R. Advani et al., 2017	Golden Hour	0%	2.7%

Safety outcomes demonstrated that symptomatic intracranial hemorrhage rates remained consistent across early time windows without significant time dependency. The ECASS III trial showed symptomatic ICH rates of 2.4% with alteplase versus 0.2% with placebo in the 3-4.5 hour

window, but mortality did not differ significantly. Extended time window treatment (4.5-24 hours) showed increased symptomatic ICH risk (OR 3.23) but comparable mortality.

Synthesis

Reconciling Heterogeneous Findings on Time-Dependent Benefit

The relationship between onset-to-needle time and recanalization success in ischemic stroke demonstrates consistent directionality across studies but with heterogeneity in effect magnitude that can be explained through several mechanisms.

Context and Population Distinctions

The observed variation in time-benefit relationships reflects fundamental differences in patient populations and treatment contexts. Studies examining IV thrombolysis alone in unselected stroke populations show more gradual decline in benefit over time compared to studies of patients with imaging-confirmed large vessel occlusion undergoing combined IVT and thrombectomy. For large vessel occlusion patients presenting directly to thrombectomy-capable centers, the benefit of bridging IVT becomes statistically non-significant after 2 hours 20 minutes, whereas for patients with smaller vessel disease receiving IVT alone, benefit extends to 4.5 hours and potentially beyond with advanced imaging selection.

The ultra-early treatment data from golden hour studies represent a distinct population context where patients reached treatment exceptionally quickly, often with milder strokes and more favorable vascular anatomy. The 44% versus 12% recanalization difference for treatment within versus beyond one hour likely reflects both the time-dependent nature of thrombolysis efficacy and selection of patients with more accessible clots.

Study Quality and Methodological Considerations

The most robust evidence derives from individual patient data meta-analyses and large registry studies with sample sizes exceeding 2,000-6,000 patients. These consistently demonstrate time-dependent benefit with quantifiable dose-response relationships. Smaller observational studies

provide supporting evidence but with wider confidence intervals and greater susceptibility to confounding.

The NINDS rt-PA Stroke Trial analysis and pooled analysis of ATLANTIS, ECASS, and NINDS established the foundational evidence that earlier treatment produces proportionally greater benefit, with odds ratios declining from 2.8 at 0-90 minutes to 1.2 at 271-360 minutes. This finding has been consistently replicated across subsequent meta-analyses.

Mechanistic Explanations for Time-Dependent Effects

The biological basis for time-dependent thrombolysis benefit involves the progressive evolution of ischemic penumbra to irreversible infarction. The rate of penumbral loss varies based on collateral circulation status, which explains why imaging-selected patients with favorable perfusion mismatch continue to benefit from reperfusion at 4.5-9 hours and even 4.5-24 hours.

For patients with large vessel occlusion undergoing thrombectomy, the diminishing benefit of bridging IVT over time reflects the pharmacokinetic reality that alteplase requires time to achieve thrombolytic effect. When groin puncture occurs rapidly after IVT administration, insufficient time has elapsed for clot lysis before mechanical retrieval begins. The interaction analysis from DIRECT-MT demonstrated that alteplase significantly increased early reperfusion when time from randomization to groin puncture exceeded 33 minutes (aOR 4.07) but not when puncture occurred sooner (aOR 1.06).

Time Threshold Recommendations

Based on the synthesized evidence, several clinically meaningful time thresholds emerge:

For IV thrombolysis alone:

- Treatment within 90 minutes provides optimal benefit (OR $\approx$ 2.8)
- Benefit remains substantial but attenuated at 90-180 minutes (OR $\approx$ 1.6)
- Treatment between 3-4.5 hours maintains efficacy (OR 1.26-1.34)

- Extended window treatment (4.5-24 hours) requires imaging selection (OR 1.42 for mRS 0-1)

For bridging IVT before thrombectomy:

- Maximum benefit when IVT administered within 1 hour of onset (aOR 1.49)
- Benefit diminishes progressively through 2 hours (aOR 1.25)
- Statistical significance lost after 2 hours 20 minutes
- When thrombectomy can be initiated within 30 minutes, bridging IVT provides minimal additional benefit

Workflow Implications

Quality improvement initiatives consistently demonstrate that door-to-needle times can be substantially reduced through systematic process changes. The implementation of comprehensive DTN reduction strategies achieved 33.77% reduction in treatment times, with post-intervention rates of DTN ≤ 60 minutes reaching 60%. Mobile stroke units further accelerated treatment, achieving tPA bolus times of 45 minutes from 911 alert compared to 76 minutes with standard EMS.

Tenecteplase demonstrates workflow advantages over alteplase, with significantly shorter door-to-needle times (30 vs 36 minutes) and door-to-puncture times (117 vs 193 minutes), attributed to its bolus administration protocol eliminating the need for infusion pumps. These time savings translate to improved clinical outcomes, with tenecteplase independently predicting NIHSS improvement at 24 hours (OR 1.715).

The evidence consistently supports that faster treatment produces better outcomes across all patient populations, treatment modalities, and time windows examined, with the magnitude of benefit declining progressively with treatment delay. The specific thresholds for clinical decision-making depend on the treatment context, available resources, and individual patient characteristics including vessel occlusion status and imaging-defined tissue viability.

DISCUSSION

This systematic review of 80 studies provides a comprehensive and nuanced synthesis of the critical relationship between onset-to-needle time (ONT) and recanalization success in acute ischemic stroke. The overarching finding is a robust confirmation of the "time is brain" doctrine, demonstrating a clear, quantifiable, and inverse correlation between treatment delay and the likelihood of achieving vessel patency. However, the discussion must move beyond this general principle to dissect the heterogeneity, understand the underlying mechanisms, and derive actionable clinical insights.

Reconciling Heterogeneity in Time-Benefit Relationships

The observed variation in effect sizes across studies is not contradictory but reflective of fundamental differences in patient populations and treatment contexts. For **IV thrombolysis alone in an unselected AIS population**, the benefit decays relatively gradually. The landmark pooled analysis by Hacke et al. (2004) established a classic dose-response: odds ratios for favorable outcome were 2.8 (95% CI 1.8-4.5) for treatment within 90 minutes, declining to 1.6 (91-180 min), 1.4 (181-270 min), and 1.2 (271-360 min). This pattern was later refined by the individual patient data meta-analysis of Emberson et al. (2014), which confirmed substantial benefit within 3 hours (OR 1.75) and a significant, though reduced, benefit in the 3-4.5 hour window (OR 1.26).

In stark contrast, for **patients with imaging-confirmed large vessel occlusion (LVO) destined for thrombectomy**, the time-benefit curve for *bridging IVT* is far steeper. The individual participant data meta-analysis by Kaesmacher et al. (2024) is pivotal, demonstrating that the benefit of adjunctive IVT diminishes rapidly as onset-to-treatment time increases. The adjusted odds ratio for improved functional outcome was 1.49 when IVT was given within 1 hour of onset, 1.25 at 2 hours, and became non-significant (aOR 1.04) at 3 hours, with a calculated loss of statistical significance at 2 hours 20 minutes. This is mechanistically plausible: for EVT to be initiated very rapidly, the pharmacological effect of alteplase may not have sufficient time to lyse the clot before

mechanical retrieval begins (Zhou et al., 2022). This creates a complex interaction where the utility of bridging therapy is conditional on the expected delay to arterial access.

The "Golden Hour" Phenomenon and Ultra-Early Recanalization

The most dramatic evidence for time-dependency comes from studies focusing on the "golden hour" ($\text{ONT} \leq 60$ minutes). Bernatowicz et al. (2016) reported a striking difference: recanalization rates of 44% with ultra-early IVT versus only 12% when treatment was administered beyond the first hour, coupled with 0% versus 23% mortality, respectively. Studies like that of Advani et al. (2017) further support that treatment within this hyper-acute window yields exceptional outcomes, including minimal disability and very low complication rates. This population likely represents a unique subset with rapid hospital arrival, often milder stroke severity, and possibly more favorable clot characteristics or collateral status, but it powerfully illustrates the upper bound of achievable benefit when systemic delays are minimized.

Extended Time Windows and the Role of Imaging Selection

A critical advancement in stroke therapy is the extension of the treatment window guided by advanced neuroimaging, moving beyond a rigid chronological clock to a "tissue clock" paradigm. For IVT, the EXTEND and EPITHET trial meta-analysis showed that reperfusion with alteplase was associated with improved functional outcomes across the 4.5 to 9-hour and wake-up stroke continuum when patients were selected based on perfusion imaging mismatch (Campbell et al., 2020). Similarly, meta-analyses of extended window thrombolysis (4.5-24 hours) continue to show benefit (OR 1.42 for mRS 0-1), albeit with a noted increase in symptomatic intracranial hemorrhage risk (OR 3.23), underscoring the necessity of careful patient selection (Rahmati et al., 2025). This confirms that while the *magnitude* of time-dependent benefit attenuates, a biological window of opportunity persists for a subgroup with favorable pathophysiology.

Workflow Optimization as a Modifiable Factor

ONT is composed of pre-hospital (onset-to-door) and in-hospital (door-to-needle, DNT) components. While the former is difficult to control, the latter is a prime target for quality improvement. This review highlights compelling evidence that systematic interventions can drastically reduce DNT. The HERMES collaboration quantified that every 15-minute reduction in DNT results in 20.3 more patients per 1000 achieving an excellent outcome (Goyal et al., 2019). Specific strategies proven effective include:

1. **Protocol Restructuring:** Pre-notification by EMS, direct transport to CT, and rapid laboratory testing can reduce DNT to under 30 minutes (Huang et al., 2016; Advani et al., 2017).
2. **Mobile Stroke Units (MSUs):** MSUs bring the CT scanner and thrombolytic capability to the patient, dramatically shortening onset-to-treatment time and improving outcomes for LVO patients (Czap et al., 2021; Tariq et al., 2023).
3. **Thrombolytic Agent Choice:** The shift to tenecteplase, administered as a single bolus, offers significant workflow advantages over the hour-long alteplase infusion. Studies show tenecteplase is associated with shorter DNT and door-to-puncture times, contributing to efficiency in bridging therapy protocols (Henderson et al., 2024; Yao et al., 2024; Singh et al., 2023).

Safety Considerations Across Time Windows

A consistent and reassuring finding across studies is that the risk of symptomatic intracranial hemorrhage (sICH) associated with IVT does not appear to increase with earlier treatment. Rates remain relatively stable across the 0-4.5 hour window (Wahlgren et al., 2008; Bluhmki et al., 2009). The increased sICH odds observed in the extended window (4.5-24 hours) highlight the altered risk-benefit calculus that must be carefully managed with imaging selection (Rahmati et al., 2025). Mortality benefits are closely tied to recanalization success and functional recovery, with ultra-early treatment showing the most profound reductions (Bernatowicz et al., 2016).

Synthesis and Clinical Implications

The evidence converges on several key actionable points:

1. **For IVT alone:** Maximum benefit is within 90 minutes, but significant benefit extends to 4.5 hours. Beyond 4.5 hours, treatment should be guided by advanced perfusion imaging.
2. **For bridging IVT before EVT:** The benefit is most pronounced when ONT is short (<2 hours). As the expected time to groin puncture shortens (e.g., in direct-to-angioplasty models), the marginal benefit of IVT decreases. Beyond ~2.5 hours from onset, the added value of bridging IVT over direct EVT becomes questionable and should be individualized.
3. **System Imperative:** Every component of the stroke care continuum, from public awareness to in-hospital protocols, must be engineered for speed. The quantifiable loss of benefit per minute of delay (Gutiérrez et al., 2025; Singh et al., 2023) mandates a relentless focus on process improvement.

The relationship between onset-to-needle time and recanalization success is fundamental, powerful, and modifiable. While biological factors set the outer limits of treatment windows, operational factors determine how much of that potential benefit is realized for each patient. The future of stroke care lies in both expanding the biological window through advanced imaging and collapsing the operational delays through systemic innovation.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review conclusively demonstrates a strong, inverse, and time-dependent relationship between onset-to-needle time and successful recanalization in acute ischemic stroke. Earlier treatment is consistently associated with higher rates of vessel recanalization, which in turn translates to significantly improved functional independence and reduced mortality. The benefit is

most dramatic within the first "golden" hour but remains substantial and statistically significant within the 4.5-hour window for IV thrombolysis. For patients receiving bridging therapy prior to thrombectomy, the added value of intravenous thrombolysis attenuates as onset-to-treatment time increases, becoming marginal beyond approximately 2 to 2.5 hours. The safety profile of thrombolysis, particularly regarding symptomatic intracranial hemorrhage, does not worsen with earlier treatment. Crucially, in-hospital workflow delays (door-to-needle time) are a modifiable factor whose reduction directly and quantifiably improves patient outcomes.

Recommendations

Based on the synthesized evidence, the following recommendations are proposed:

1. **For Clinical Practice:** Adopt a tiered approach to time assessment. Prioritize hyper-acute treatment (ONT < 90 min) as the highest goal. In the 3-4.5 hour window, IVT remains standard. For extended windows (4.5-24 hours) or wake-up strokes, IVT should be guided by advanced perfusion/penumbra imaging (Campbell et al., 2020; Hill, 2021). For LVO patients eligible for EVT, the decision for bridging IVT should factor in the estimated time to groin puncture; if puncture is expected within 30-45 minutes of IVT start, the benefit may be minimal (Zhou et al., 2022).
2. **For Stroke Systems of Care:** Implement and continuously refine standardized, parallel-processing protocols to minimize door-to-needle time, targeting benchmarks of ≤ 30 minutes for a majority of patients. Consider the adoption of tenecteplase as the preferred thrombolytic agent to streamline administration (Henderson et al., 2024). Where feasible, invest in mobile stroke unit programs to address pre-hospital delays, especially in metropolitan areas (Czap et al., 2021).
3. **For Quality Improvement & Research:** Establish robust monitoring of key time metrics (ONT, DNT, onset-to-reperfusion). Future research should focus on refining imaging biomarkers that better predict recanalization likelihood and clinical benefit at individual

patient levels, particularly in extended time windows and for deciding on bridging therapy. Further studies are needed on the cost-effectiveness of system-wide interventions like MSUs.

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