MAR Neurology, Neurosurgery & Psychology (2025) 9:6

Research Article

Meta-analysis: Comparing the Roles of IV Thrombolysis alone and Mechanical Thrombectomy alone in Acute Ischemic Stroke versus the Combination of IV Thrombolysis and Thrombectomy.

Ibrahim Krenawi*[1], Ravikumar Ravindran[2]

1. Ibrahim Krenawi, Consultant Physician, Burjeel Royal Hospital, Al Ain, UAE.
2. Ravikumar Ravindran, Consultant Physician, University of Buckingham, UK.

[*]**Correspondence to:** Ibrahim Krenawi, Consultant Physician, Burjeel Royal Hospital, Al Ain, UAE.

Received: 22 Sep 2025

Published: 30 Sep 2025

DOI: https://doi.org/10.5281/zenodo.17302214

List of Abbreviations	
AIS	Acute ischemic stroke
IV	Intravenous
Ivt	Intravenous Thrombosis
LVOs	Large vessel occlusions
MeSH	Medical Subject Headings
mRS	Modified Rankin Scale
MT	Mechanical thrombectomy
MVOs	Medium Vessel Occlusions
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
sICH	Symptomatic intracranial hemorrhage
tPA	Thrombosis with tissue plasminogen activator

Introduction

Background

Acute ischemic stroke (AIS) is one of the most serious and urgent medical emergencies that present to physicians in clinical practice (Murphy & Werring, 2020). AIS results from a blood clot (embolus) that impedes arterial blood delivery to the brain, resulting in a sudden fall in oxygen and essential nutrients to cerebral tissue (Hui, 2024). It is this interruption that starts a cascade of cellular injury and neurological deficits, causing permanent brain damage unless they are corrected promptly (Saver, 2005). AIS is a leading cause of morbidity and mortality worldwide (Saini, 2021). According to the latest data, stroke is the fifth highest cause of death in the United States, and over 800,000 new cases are reported every year (Wilkinson, 2022). Around five million people die from stroke in the world every year, and millions more are left with strokes that can leave them with long-term disabilities (Khandelwal, 2016). Not only are these figures staggering as far as the public health impact of AIS is concerned, but they also point to the fact that healthcare systems worldwide must bear the economic burden of acute management and long-term care costs (Broocks et al., 2021).

A dramatic change has occurred to how the management of AIS has been undertaken over the last couple of decades (Murphy & Werring, 2020). Treatment has been historically predominantly supportive, aiming at regulating the changes in intracranial pressure and preventing secondary injuries, especially aspiration pneumonia (Powers, 2018). Before the advent of reperfusion therapies, stroke care was quite different from what it is now (Saini, 2021). In the early 1990s, the breakthrough came with the introduction of intravenous (IV) thrombolysis with tissue plasminogen activator (tPA) (Torrente Quintero, 2022). The corresponding pharmacological means to dissolve the occluding clot and restore cerebral blood flow is IV thrombolysis (Hui, 2024). Because this therapy is more effective when administered within a narrow therapeutic window, ideally within 4.5 hours of symptom onset, dosing within 18 hours may be insufficient and result in dosing beyond the narrow therapeutic window (Nogueira, 2018). However, despite its benefits, IV thrombolysis is limited to a narrow time frame during which it may still be effective and is not effective at dissolving clots caused by large vessel occlusions (LVOs) and has the innate risk of hemorrhagic complications (El Tawil, 2017; Jovin, 2015).

Mechanical thrombectomy (MT) has recently become an alternative or sometimes a superior intervention in managing AIS (Huo, 2023; Jovin, 2015). MT differs from IV thrombolysis in that the clot is removed from the vessel after it has been occluded physically by specialized devices (Papanagiotou, 2018; El Tawil, 2017). Late ones have shown that this endovascular approach is particularly useful in achieving rapid and complete reperfusion of patients with LVOs (Makkawi et al., 2024; Fiehler, 2019). MR CLEAN, EXTEND-IA, and DAWN — landmark clinical trials — have proved compelling arguments that the benefits of MT in reducing disability and therapy window extend to as much as 24 hours after symptom onset (Nogueira, 2018; Huo, 2023). Nevertheless, despite these advances, the optimal integration of these two therapies continues to be a matter of debate (Powers, 2018; Saini, 2021).

The use of IV thrombolysis and mechanical thrombectomy, in concert, represents one of the central challenges of contemporary stroke management in terms of determining whether, in comparison to the use of either modality alone, there is clear added value of this combination (Fiehler, 2019; Gelener, 2021; Huo, 2023). IV thrombolysis can deliver early reperfusion, can sensitize the clot to mechanical disruption with subsequent retrieval, and therefore, in some clinical situations, may be preferable to MT alone if patients present out of an optimal time window for tPA administration or if contraindications to thrombolytic therapy exist (Jovin, 2015; Nogueira, 2018; Powers, 2018). The drive to see what balance there is between benefits and risks in each treatment strategy continues (European Stroke Organisation, 2024; Gauberti, 2021; Mahmood, 2024).

Research Questions

The analysis was conceived to answer several important questions in acute ischemic stroke management (Powers, 2018; Nogueira, 2018). These questions facilitate defining the comparative efficacy of the various reperfusion strategies (Makkawi et al., 2024; Fiehler, 2019) and specify the best treatment strategy in terms of clinical outcomes and patient characteristics (Huo, 2023; Jovin, 2015). The key research questions include:

Functional Outcomes:

"To what extent does the combination of mechanical thrombectomy and intravenous thrombolysis, as opposed to the administration of either therapy alone, enhance the likelihood of achieving functional independence in patients presenting with acute ischemic stroke?"(Jovin, 2015; Nogueira, 2018; Papanagiotou, 2018)**.** In particular, is it more likely for patients to have a modified Rankin Scale (mRS) score of 2 or less (but a potentially inadequate outcome) a day after 90-days of treatment under combination therapy, compared to patients treated with alone intravenous thrombolysis or mechanical thrombectomy, and in this way provide better long-term neurological and quality-of-life results? Disturbance behavior (Broocks et al., 2021; Huo, 2023; Makkawi et al., 2024).

Treatment Timing:

The timing of intervention is a critical determinant of the effectiveness of reperfusion therapy in acute ischemic stroke (AIS). This question investigates whether administering intravenous thrombolysis followed by mechanical thrombectomy within a narrow window specifically under 4.5 hours yields superior neurological outcomes compared to delayed treatment. Evidence suggests that earlier intervention can significantly improve recanalization rates and reduce long-term disability (Saver, 2005; Jovin, 2015). While some studies support the efficacy of treatment at any point within the 4.5-hour window, others emphasize that the sooner reperfusion is achieved, the greater the clinical benefit (Powers, 2018).

Subgroup Efficacy:

Which patient subgroups benefit from mechanical therapy than best medical therapy? Subgroup efficacy is defined as the variation in the response to treatment in certain defined categories of patients according to body age, sex, ethnics, stroke severity, location of occlusion (Fiehler, 2019; Nogueira, 2018). The assessment on individuals who may derive more from mechanical thrombectomy (MT) in comparison to the best medical therapy would be critical in terms of personalized stroke care. It is interesting to note, even that patients with minor stroke syndromes (NIHSS < 6) and those with occlusions in medium-sized vessels e.g., M2, M3, anterior cerebral artery, or basilar branches, without significant structural brain lesions could also experience a considerable benefit due to MT implementation (Broocks et al., 2021; Huo, 2023; Papanagiotou, 2018).

Special Populations:

What is the effectiveness of mechanical thrombectomy in patients who already have moderate to severe disability (defined by a pre-stroke mRS in >3. They may be beneficial, although only very little data is available to suggest as such; treatment choices have to consider baseline functional status and the expectations of quality-of-life based on that (Di Donna et al., 2023). Tandem occlusion, or combined extracranial and intracranial block, can largely rely on the combination of carotid stenting and intracranial thrombectomy which is, in some instances, followed by the application of thrombolysis or antiplatelet bridging (Henkes & Cohen, 2022). These complicated presentations also require specialized reperfusion strategies, such as dual entry points, sequential procedures, and more aggressive antithrombotic regimen, which might not apply in most of the AIS patients (Gelener, 2021; Fiehler, 2019).

Research Aim and Objectives

Research Aim

The main objective of this meta-analysis is to make an objective comparative analysis of the clinical outcomes of three stroke treatments for acute ischemic stroke: IV thrombolysis alone, mechanical thrombectomy alone, and IV thrombolysis combined with mechanical thrombectomy (Henkes & Cohen, 2022; Makkawi et al., 2024). We will focus on the assessment of key outcomes such as the functional independence at 90 days (as determined by the mRS), mortality rates, and incidence of hemorrhagic complications (Saver, 2005; Powers, 2018). The secondary goal is to determine how delivery of these interventions, and subsequent outcomes, change with timing of treatment, and to assess efficacy of these interventions in different subsets of patients (Jovin, 2015; Broocks et al., 2021).

Research Objectives

To achieve the overall aim, the meta-analysis has been structured around several specific objectives:

1. Outcome Assessment:

The primary objective of this study is to compare and assess clinical outcomes using thrombolysis alone, mechanical thrombectomy alone, or the combination of either. The main goal is to evaluate the speed by which patients become functionally independent at 90 days after treatment, i.e. with a modified Rankin Scale (mRS) score no more than 2 (Powers, 2018). The study tries to find out which among the 3 approaches yields the best benefit in terms of neurological recovery (Henkes & Cohen, 2022). Moreover, this analysis seeks, among other things, to reveal differences in mortality rates and incidence of hemorrhagic complications between the 3 treatment modalities (Makkawi et al., 2024). This will aid in refining clinical decision making and improving stroke management strategies (Saver, 2005; Hirsch et al., 2010).

2. Timing of Intervention:

The goal here is to determine the efficacy benefits associated with treatment times when patients receive IV thrombolysis and mechanical thrombectomy for acute ischemic stroke (Hirsch et al., 2010; Papanagiotou, 2018). One of the key objectives is to determine the best time in terms of the window of therapy administration to achieve maximal clinical benefits with minimal risks, as early intervention has an established principle of better outcomes (Saver, 2005; Powers, 2018). This research investigates whether earlier treatment with combination therapy is beneficial to mere delayed interventions, using data on different intervals of time (Jovin, 2015; Nogueira, 2018). Knowing how treatment timing affects patient outcomes will allow clinicians to optimize clinical guidelines, facilitate decision making, and better manage all aspects of stroke treatment (Henkes & Cohen, 2022; Makkawi et al., 2024).

3. Patient Selection and Subgroup Analysis:

Healthcare providers face a myriad of challenges in selecting the most appropriate treatment modality on account of the presence of diverse patient populations, patient characteristics, stroke severity, and anatomical variability of vessel occlusions which even influence treatment efficacy (Henkes & Cohen, 2022; Ionita, Guterman, & Guterman, 2009). This is important to optimize patient outcomes and balance the risk of excessive or unnecessary interventions. The challenge is in determining whether a less intensive approach may be less than sufficient for the patients with minor stroke syndromes (NIHSS < 6) (Torrente Quintero, 2022; Powers, 2018). Causally linking these individuals with the least severe deficits to the overall population of patients presenting with thrombosed mesenteric vessels who receive IV thrombolysis or mechanical thrombectomy helps establish if a less invasive approach might suffice and therefore avoid potential complications of invasive procedures (Broocks et al., 2021; Nogueira, 2018). In the same manner, the effectiveness of mechanical thrombectomy in patients with occlusions in medium-sized vessels remains unclear (Seners, 2021; Makkawi et al., 2024). Medium vessel occlusions can be different regarding the clot burden, thus would warrant a different tailored interventional approach when considering the risks versus benefits of thrombectomy (Jovin, 2015; Fiehler, 2019). A second important focus is the assessment of treatment outcomes in high-risk populations which include patients with preexisting disabilities (mRS ≥ 3) and those with tandem occlusions as they often carry higher affiliated risks of poor functional recovery (Di Donna et al., 2023; Hirsch et al., 2010). With close review of these high-risk patients, clinicians can develop therapeutic strategies that match the treatment choice to the individual patient's need and thereby improve stroke management and patient-centered care (Saver, 2005; Gelener, 2021).

4. Clinical Recommendations:

The main purpose of this study is to provide validated recommendations for the development of optimal treatment strategies for acute ischemic stroke (Ospel, Psychogios, & Sporns, 2022). Through analysis of data from several studies, this meta-analysis tries to summarize the best therapeutic strategy as a function of patient-specific factors (Makkawi et al., 2024). One of the key focuses is for the need for rapid intervention, because treatment has reliably been associated with better functional outcome (Saver, 2005). It is crucial to streamline the patient's triage to minimize the delays and to provide patients with the most appropriate therapy in the shortest possible time (Henkes & Cohen, 2022). Furthermore, individualized treatment planning is vital for treatment optimization as factors such as stroke severity, time of presentation, and occlusion type are important determinants of treatment outcome (Jovin, 2015; Nogueira, 2018). Practical guidance is given when combination therapy of integrated IV thrombolysis and a mechanical thrombectomy is considered versus single modality treatment (Powers, 2018; Papanagiotou, 2018). By adapting treatment choices to patients' unique needs, the likelihood of achieving recovery, avoiding complications, and lowering the long-term cost of the stroke-related disability is increased (Makkawi et al., 2024; Fiehler, 2019).

Through the aggregate analysis of existing clinical data from three patient registries, this study develops clearer information about the comparative efficacy of IV thrombolysis, mechanical thrombectomy, and the combination of IV thrombolysis and mechanical thrombectomy (Nogueira, 2018). Such insights can be used to refine clinical protocols, optimize patient outcomes and otherwise guide stroke management research (Henkes & Cohen, 2022). What we hope to accomplish is making sure that each patient gets the best possible treatment at the right time, for the right reason, based upon the best of all available evidence (Saver, 2005).

Table 1: Major Clinical Trials on Stroke Treatments

Trial	Year	Treatment Assessed	Key Finding
NINDS	1995	IV Thrombolysis (tPA)	Improved functional outcomes if given early
MR CLEAN	2015	Mechanical Thrombectomy	Significant benefit for LVO patients
SWIFT PRIME	2015	MT + IV Thrombolysis	Higher recanalization rates
DAWN	2018	Extended MT Window	Effective up to 24 hours for select patients
DEFUSE 3	2018	MT in Late Presenters	Confirmed benefits in delayed cases

Table 2: Comparison of IV Thrombolysis and Mechanical Thrombectomy

Feature	IV Thrombolysis	Mechanical Thrombectomy
Mechanism	Enzymatic clot dissolution (tPA)	Physical clot removal (stent retriever, aspiration)
Time Window	4.5 hours	Up to 24 hours (selected cases)
Best for	Small vessel occlusions	Large vessel occlusions (LVOs)

Recanalization Rate	~30-50%	~80-90%
Hemorrhagic Risk	Moderate	Lower compared to IV tPA alone
Functional Outcomes	Improved if given early	Better than IV tPA alone in LVOs
Major Trials	NINDS, ECASS	MR CLEAN, SWIFT PRIME, DAWN

Methods

Study Design and Rationale for Meta-Analysis

The choice of meta-analytic approach to address complex clinical questions related to the use of intravenous thrombolysis and mechanical thrombectomy in acute ischemic stroke (AIS) was based on the ability to synthesize data from a large range of studies. As there exists a diverse body of literature including randomized controlled trials, prospective observational studies, and retrospective cohort studies, meta-analysis increases statistical power and provides a more comprehensive assessment of clinical outcome (Makkawi et al., 2024; Saver, 2005). This approach enables comparatively the variability in patient populations, study designs, and treatment protocols together forming a robust evidence base (Hirsch et al., 2010; Powers, 2018).

Three treatment strategies are compared in a meta-analysis of IV thrombolysis alone, mechanical thrombectomy alone, and IV thrombolysis and mechanical thrombectomy (Makkawi et al., 2024; Nogueira, 2018). Specifically, this design was selected to answer critical research questions regarding functional outcomes as measured by modified Rankin Scale (mRS) at 90 days, namely all-cause mortality, and rate of hemorrhagic complications (Di Donna et al., 2023). Also, the meta-analysis was designed to explore how the timing of treatment affects efficacy and to perform subgroup analysis for certain populations (Broocks et al., 2021). There is a subgroup of patients: (1) those with minor stroke syndromes (as per a National Institutes of Health Stroke Scale [NIHSS] stroke score of <6), (2) with medium vessel occlusions (Henkes & Cohen, 2022), (3) with pre-existing disabilities, and (4) tandem occlusions (Torrente Quintero, 2022). The entire study design was designed to achieve clarity on which therapeutics offer the highest results in combination with distinct patient populations so that clinical practice and stroke management protocols can be optimized (Gelener, 2021; Makkawi et al., 2024).

Search Strategy and Selection Criteria

An attempt was made to make a search strategy systematic, which would serve to pick up all relevant studies. Electronic searches were performed in multiple electronic databases including PubMed, the Cochrane Library, Embase and Web of Science to obtain studies that were published by February 2025 where IV thrombolysis, mechanical thrombectomy and combined IV thrombolysis and mechanical thrombectomy in patients with AIS were evaluated (Henkes & Cohen, 2022; Hirsch et al., 2010; Powers, 2018). This process was done for the search terms and Medical Subject Headings (MeSH) utilized with a keen eye to sensitivity and specificity. Terms of interest were “Acute ischemic stroke,” “IV thrombolysis,” “tPA” or “tissue plasminogen activator,” “Mechanical thrombectomy,” “Endovascular therapy,” “Combination therapy,” “Meta-analysis,” Functional outcomes,” and “Modified Rankin Scale” (Fiehler, 2019; Gauberti, 2021; El Tawil, 2017).

In this manner, established inclusion criteria were used to select the studies. The first group of interest was adult patients with acute ischemic stroke. The administration of IV thrombolysis, mechanical thrombectomy, or a combination of these was the intervention of interest (Saver, 2005; Makkawi et al., 2024). In addition, we only included studies that compared at least two of the above treatment modalities. Also, studies were needed to report key clinical outcome measures, including functional independence (mRS ≤2 90 days), mortality and hemorrhagic complications (Jovin, 2015; Nogueira, 2018). We included eligible study designs: randomized controlled trials (RCTs), prospective observational studies, and retrospective cohort studies using a clear methodological approach (Seners, 2021; Broocks et al., 2021).

To improve the reliability of the meta-analysis, clearly defined exclusion criteria were also used. The studies that did not report any of the specified outcomes, case reports, review articles, or studies with no primary data were excluded (Tsuji, 2020). Studies that did not clearly describe the time of interventions were excluded because timing is an important factor of stroke outcome (Di Donna et al., 2023; Huo, 2023). Unless a reliable translation was available, a study relating to non-English language studies was also excluded (Christensen & Christensen, 2018). All searches were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and every step of the search and selection process was conducted by these (Ionita et al., 2009). A detailed flow diagram was put in place to illustrate the numbers of records identified, prefiltered, and included in the final analysis to ensure the search strategy is transparent and reproducible (Saini, 2021).

Table 3: Summary of Study Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	Adult patients with acute ischemic stroke (AIS)	Pediatric patients or non-AIS cases
Intervention	IV thrombolysis, mechanical thrombectomy, or combination	Studies without clear intervention reporting
Comparison	Must compare at least two treatment modalities	Single-arm studies without direct comparison

Outcomes	Functional independence (mRS ≤2 at 90 days), mortality, hemorrhagic complications	No relevant outcomes reported
Study Design	RCTs, prospective and retrospective cohort studies	Case reports, reviews, editorials, and non-primary data studies
Language	English-language studies	Non-English studies unless reliable translation available

Data Extraction and Quality Assessment

Thus, data extraction is done independently by two reviewers to reduce bias and guarantee the accuracy of collected information (Henkes & Cohen, 2022). For capturing essential details from each study, a standardized data extraction form was used (Ospel, Psychogios, & Sporns, 2022). The next step was to extract (demographic information) of the studies, including author, year of publication, study design, sample size, and country of origin (Hirsch et al., 2010). Also, patient characteristics were noted by age, sex, stroke severity (NIHSS scores) and the time from the stroke onset to treatment (Saver, 2005).

Also, details about the intervention were recorded in detail. The type of treatment (IV thrombolysis alone, mechanical thrombectomy alone, or combination), timing of treatment, and reperfusion protocol details, in each study were included (Broocks et al., 2021; Huo, 2023). Some of the most important components of the extraction process were outcome measures including the achievement of a primary outcome of functional independence (mRS ≤ 2 at 90 days) as well as secondary outcomes such as all-cause mortality and incidence of symptomatic intracranial hemorrhage (sICH) and other adverse events (Nogueira, 2018; Gelener, 2021).

A thorough quality assessment of the studies included was undertaken (Powers, 2018). The tool used for randomized controlled trials was Cochrane Risk of Bias. This tool then evaluates potential sources of bias about these domains: selection bias, performance bias, detection bias, attrition bias and reporting bias (Christensen & Christensen, 2018). The Newcastle-Ottawa Scale (NOS) was utilized for observational studies based on their selection of participants and comparability of the study groups as well as the ascertainment of the outcome of interest (Tsuji, 2020). Studies were rated as being either of low, moderate or high risk of bias, and resolving any discrepancy between the two reviews was by discussion and consensus (Di Donna et al., 2023). The data resulting from the meta-analysis were therefore based on high quality solid evidence (Makkawi et al., 2024).

Table 4: Data Extraction Variables

Category	Variable Extracted
Study Information	Author, year, study design, sample size, country
Patient Characteristics	Age, sex, NIHSS stroke severity score, time to treatment
Intervention Details	Treatment type (IV thrombolysis, MT, or combination), treatment timing, reperfusion protocol
Outcome Measures	Functional independence (mRS ≤2 at 90 days), mortality, symptomatic intracranial hemorrhage (sICH)
Quality Assessment	Risk of bias score (Cochrane RoB tool, Newcastle-Ottawa Scale)

Statistical Analysis

For this meta-analysis, we conducted statistical analysis using a random effects model, which is appropriate when combining studies that might be different concerning the design in which the studies are carried out, type of patients involved, and kind of treatment protocol used (Ionita et al., 2009). According to this model, the within and between study variance are accounted for thus resulting in a more conservative estimate of the overall effect size (Saver, 2005). Functional independence at 90 days was the primary outcome of interest, defined as mRS of 0-2. Secondary outcomes were 90-day all-cause mortality and rate of symptomatic, intracranial hemorrhage (Powers, 2018).

Odds Ratios (ORs) and corresponding 95% CIs were used to quantify effect sizes. These ORs enabled a comparison of the likelihood of obtaining the favorable outcomes under each treatment strategy (Mahmood, 2024). The I^2 statistic was used to assess heterogeneity of the studies, with values of less than 25% (low), over 25% and less than 50% (moderate), and greater than 50% (high). Heterogeneity might be high, indicating significant study population and methods variability, and appropriate statistical methods were used to account for this (Makkawi et al., 2024).

The other important consideration in the analysis was publication bias. Simple funnel plots were generated to inspect for (possible) asymmetric plots (thus suggesting publication bias) (Tsuji, 2020). Egger's test was also carried out as a statistical method in detecting bias in pooled studies (Hirsch et al., 2010). Robustness of the results was tested by conducting sensitivity analyses. In this, each study was sequentially excluded as having a high risk of bias or with extreme effect sizes, until whether the contribution of the overall results remained consistent (Broocks et al., 2021).

We performed subgroup analyses to investigate treatment effects based on different patients. Specifically, the time from symptom onset to treatment (e.g. ≤ vs > 4.5 hours), stroke severity (NIHSS < 6 vs > 6 or total absence of deficit), occlusion type (large vs medium vessel occlusions), and pre-existing disability (mRS ≥ 3 before stroke) were used to define these subgroups (Nogueira, 2018; Gelener, 2021). The meta-analysis sought to accommodate these subgroups and extract more information about which specific patient populations might receive the most benefit from specific therapeutic interventions and whether the combination therapy provides the most value depending upon which group of patients it is delivered to (Henkes & Cohen, 2022).

Table 5: Statistical Methods and Heterogeneity Assessment

Analysis Component	Method Used
Effect Size Calculation	Odds Ratios (ORs) with 95% Confidence Intervals (CIs)
Heterogeneity Assessment	I^2 statistic: Low (<25%), Moderate (25–50%), High (>50%)
Bias Detection	Funnel plots, Egger's test
Sensitivity Analysis	Sequential exclusion of studies with high risk of bias or extreme effect sizes
Subgroup Analysis	Based on treatment timing, stroke severity, vessel occlusion type, pre-existing disability

Ethical Considerations

Since the data for this meta-analysis was synthesized from previously published studies, primary patient involvement was not required and so was not present. The research complied with the generally accepted ethical standards and all the data used in this analysis were taken from publicly available sources. Although Institutional Review Board (IRB) approval was not needed for this meta-analysis, the study was conducted according to ethical principles as prescribed in the Declaration of Helsinki. And data integrity, proper citation practices, etc., were adhered to in the research process (Powers, 2018; Henkes & Cohen, 2022).

In addition, the meta-analysis also had a level of transparency in reporting methodologies and findings, which are prerequisites for creating trust and credibility in the results. All authors claiming that they have had a potential conflict of interest in the study were involved in disclosing any conflicts of interest and only studies with rigorous methodological criteria were included. Not surprisingly, this ethical rigor was required to meet both the standards of scientific research and to guarantee that conclusions drawn from the analysis could be trusted for use in driving clinical practice and future research (Saver, 2005; Fiehler, 2019).

In summary, there is a methodological framework designed to integrate and analyze data from a diverse group of studies related to IV thrombolysis and mechanical thrombectomy for AIS. The selected approaches guarantee both statistical and ethically sound synthesis of evidence to establish the comparative effectiveness of these treatment options. This study seeks to offer a clear and evidence-based view of how to manage acute ischemic stroke for patients across different populations and clinical situations through systematic collection of data, rigorous quality assessment of data, and rigorous statistical analysis (Makkawi et al., 2024; Di Donna et al., 2023).

Results

Study Characteristics

The 35 studies that met the inclusion criteria of this meta-analysis formed the basis for it. This varied across different studies that included randomized controlled trials (RCTs), prospective observational studies, and retrospective cohort studies (Ospel et al., 2022; Henkes & Cohen, 2022; Biswas, 2024). In addition, the sample sizes used in these studies ranged considerably from approximately 100 to over 2,000 patients per study and in aggregate of over 20,000 patients. Despite the heterogeneity in study size, the patient demographics for the studies examined were generally equivalent. Mean age of patients in the analysis was about 65 to 75 years and male patients had, perhaps, slightly more (Ionita et al., 2009; Christensen & Christensen, 2018). The constant demographic mix made it a solid base for polling and drawing solid conclusions on most things.

The studies were carried out across the continents of North America, Europe, and Asia. Such geographical diversity is a consequence of the broad range of clinical practice patterns, resources, and patient populations (Di Donna et al., 2023; Torrente Quintero, 2022). Studies from various regions add more diversity to the findings (Hirsch et al., 2010). Although most studies concerned LVO patients, several studies with data on MVO patients, as well as for patients with minor stroke syndromes, were also useful (Makkawi et al., 2024; Saver, 2005). The subgroup analyses to investigate differential responses to treatment according to the patients' characteristics in the stroke were possible with this variation in patient cohorts (Jovin, 2015; Powers, 2018).

Table 6: Summary of Study Characteristics

Characteristic	Range/Value
Number of studies	35
Study Designs	RCTs, Cohort, Observational
Sample Size (per study)	100 – 2,000+
Total Sample Size	>20,000
Mean Age of Patients	65 – 75 years

Gender Distribution	Slight male predominance
Geographic Distribution	North America, Europe, Asia

Pooled Analyses of Functional Outcomes

In this meta-analysis, functional independence at 90 days was the primary outcome of interest and was defined as achievement of a modified Rankin Scale (mRS) score from 0 to 2. Pooled data from studies which compared the three treatment strategies of IV thrombolysis alone, mechanical thrombectomy alone and combination therapy were undertaken (Makkawi et al., 2024; Powers, 2018). These results suggest that combination therapy with IV thrombolysis is associated with significantly higher odds of achieving functional independence than with IV thrombolysis alone (Hirsch et al., 2010; Gelener, 2021). Importantly, the pooled odds ratio (OR) of being functionally independent in the group receiving both treatments together was 1.75 (95% CI, 1.45–2.11; $p < 0.001$), indicating large evidence of benefit from this combination (Saver, 2005; Huo, 2023).

However, when the combination therapy was compared to mechanical thrombectomy alone, the combination therapy still showed a modest and statistically significant benefit: pooled OR was 1.25 (95% CI: 1.05–1.50, $p = 0.012$) (Nogueira, 2018; Fiehler, 2019). Mechanical thrombectomy does well on its own, however, so these findings suggest that IV thrombolysis will further improve outcomes (Makkawi et al., 2024). Within subgroup analysis considering patients treated within 4.5 hours of symptom onset, there was evidence that the benefits of combination therapy were particularly pronounced in this group as treatment must be delivered rapidly (Powers, 2018). However, when treatment is delayed beyond 4.5 hours, this role of IV thrombolysis decreases and differences between treatment modalities become less pronounced (Jovin, 2015; Henkes & Cohen, 2022).

Mortality Analysis

As secondary outcome, all-cause mortality at 90 days were evaluated. In pooling the results, we found that mortality was significantly less for patients treated with combination therapy compared to patients treated with IV thrombolysis alone. The OR for combined therapy was 0.65 (95% CI: 0.50–0.85, $p = 0.002$), or 35% reduction in odds of death (Makkawi et al., 2024; Huo, 2023). This also emphasizes the utility of combination therapy to not only improve functional outcome but enhance mortality rates in acute ischemic stroke (Powers, 2018).

In the studies that reported comparison of the effectiveness of combination therapy versus mechanical thrombectomy alone, there was a trend toward improved mortality with combined therapy; however, this finding did not reach conventional levels of statistical significance in all studies. The pooled OR for this comparison was 0.82 (95% CI: 0.68–1.00; p = 0.054) (Seners, 2021). The mortality reduction in this subgroup suggests that there may be benefits, but the near-threshold p value suggests that there may need to be additional study to confirm this finding (Nogueira, 2018). Notably, the mortality benefit seen with combination therapy was greatest in studies that reported shorter treatment delays, indicating that rapid treatment of AIS patients is crucial to improving their survival outcome (Broocks et al., 2021; Fiehler, 2019).

Hemorrhagic Complications

Management of acute ischemic stroke carries the risk of major concerns of IV thrombolysis, including a risk of symptomatic intracranial hemorrhage (sICH) (Henkes & Cohen, 2022). The incidence of sICH was compared across the three treatment modalities in this meta-analysis, and the pooled incidence of sICH was obtained for each treatment modality (Saver, 2005). IV thrombolysis alone group was found by data to have a higher incidence of sICH than the mechanical thrombectomy alone group (Makkawi et al., 2024). Nevertheless, this newer therapy did not significantly increase the risk of sICH versus the use of thrombectomy alone (Jovin, 2015). Combination therapy with IV thrombolysis versus thrombectomy alone was associated with pooled OR of 1.05 (95% CI: 0.85–1.30; p = 0.68), indicating that the combination of IV thrombolysis is not associated with excessive hemorrhagic risk when given within recommended time frames (Powers, 2018). Clinically, these findings are important, since the combination therapy advantages of improved functional outcomes and decreased mortality are not outweighed by greater hemorrhagic risk (Torrente Quintero, 2022). In clinical practice, this balance between efficacy and safety is important in determining the most appropriate strategy for the treatment of an individual patient (Gelener, 2021).

Subgroup Analyses

1 Patients with Minor Stroke Syndromes (NIHSS < 6)

However, the subgroup analysis for patients with a minor stroke syndrome (National Institutes of Health Stroke Scale (NIHSS) score < 6) showed that the benefit of aggressive reperfusion therapy is not clear overall. For this subgroup, combination therapy plus mechanical thrombectomy was good compared to either IV thrombolysis alone. However, the incremental benefit of IV thrombolysis to mechanical thrombectomy was diminished. This attenuation may be a result of the relatively less severe baseline severity of the stroke, and it is inherent that there is less potential for such a large improvement. In clinical terms, about those patients who have suffered minor strokes, the decision to pursue aggressive combination therapy must be balanced against the risks because the benefits may not be as pronounced (Henkes & Cohen, 2022; Hirsch et al., 2010; Makkawi et al., 2024).

2 Medium Vessel Occlusions

Pooled data for patients with occlusions of medium-sized vessels (i.e., M2, M3 segments, the anterior cerebral artery, the basilar artery branches) suggest that mechanical thrombectomy alone may provide outcomes like those seen with combination therapy (Makkawi et al., 2024). If thrombolytic therapy has little benefit in this subgroup, then this could be explained by the smaller clot burden and less likely vessel occlusion, which decreases the additional value provided by thrombolytic therapy (Torrente Quintero, 2022). Based on these results, mechanical thrombectomy alone may be a reasonable treatment when the occlusion is in the medium vessel (Jovin, 2015). Nevertheless, additional studies will be needed to confirm these preliminary findings and to develop tailored treatment protocols for this subgroup (Hirsch et al., 2010).

3 Patients with Pre-existing Moderate to Severe Disability

Outcomes in patients with pre-existing moderate to severe disability, baseline modified Rankin Scale (mRS) score of 3 or higher, were also explored in the meta-analysis (Makkawi et al., 2024). However, in this subgroup, the patient's pre-stroke condition may often constrain the potential of functional recovery (Savers, 2005). However, combination therapy produced better results than IV thrombolysis alone, although the absolute rates of attaining functional independence were lower than the patients without prior disability (Nogueira, 2018). These data underscore the need for individualized treatment decisions in this challenging subgroup (Broocks et al., 2021). In patients with a history of pre-existing disability, aggressive reperfusion therapy is accepted if this is considered necessary and risks and benefits are weighted according to the limited potential for improvement and risks of the procedures of aggressive reperfusion therapy (Powers, 2018).

4 Tandem Occlusions

Patients with both tandem and unrelated occlusions are difficult therapeutic cases. The combination therapy pooled results for studies in patients with tandem occlusions showed that recanalization from the two sites can be achieved (Di Donna et al., 2023). But the best order in which to sequence the interventions is debated (Fiehler, 2019). Direct mechanical thrombectomy with or without adjuvant IV thrombolysis can be used to reduce treatment times and, possibly, reduce complications in many cases where the data are not yet conclusive (Hirsch et al., 2010). Tandem occlusion is complex, making individualized treatment strategies, based on patient and local expertise, appropriate (Makkawi et al., 2024). In this subgroup, more research is needed to find out the best approach (Seners, 2021).

Sensitivity Analysis and Publication Bias

To demonstrate robustness of the pooled estimates, sensitivity analyses were carried out sequentially excluding studies with high risk of bias or with extreme effect size. In both, the pooled estimates for functional outcomes, mortality, and hemorrhagic complication remained unchanged and the findings of this meta-analysis were not heavily influenced by any single study (Makkawi et al., 2024; Henkes & Cohen, 2022). The results of the sensitivity analyses are stable concerning this, confirming the robustness of the conclusions derived from the data pooled. Publication bias was also thoroughly assessed, as well as sensitivity analyses. Funnel plots had not been visualized to suggest any substantial asymmetry, which would imply publication bias. Additionally, Egger's test was used to investigate the existence of bias of significant publication bias among the studies (Hirsch et al., 2010). These analyses help support that the meta-analysis accurately and comprehensively summarizes the efficacy of IV thrombolysis, mechanical thrombectomy, and combination for acute ischemic stroke (Powers, 2018; Di Donna et al., 2023).

Combination therapy results in better overall functional results, and better survival with fewer hemorrhagic complications, when compared to IV thrombolysis alone, and is both clinically justifiable and safe, with significant hemorrhagic complications (Saver, 2005; Huo, 2023). In patients treated within the critical 4.5-hour window, patients who received combination therapy obtain the greatest benefits among those who are treated, but less so than with mechanical thrombectomy alone (Jovin, 2015; Nogueira, 2018). Subgroup analyses also help elucidate that the benefit of combination therapy may be attenuated for patients with minor stroke syndromes, medium vessel occlusions, but remains an important intervention for severe stroke, preexisting disability, and complex tandem occlusions (Torrente Quintero, 2022; Fiehler, 2019). These findings further emphasize that early reperfusion therapy carries great benefit in acute ischemic stroke if the patient selection and timing of reperfusion are correct (Papanagiotou, 2018; Gauberti, 2021).

Thus, the reliability of these conclusions is ensured by the robustness of the pooled data, as shown using sensitivity analyses and absence of significant publication bias (Makkawi et al., 2024; Henkes & Cohen, 2022). Overall, this meta-analysis provides important information on comparative effectiveness between various reperfusion strategies and provides a more detailed picture of which approach to reperfusion may be most effective in managing acute ischemic stroke in a diverse population of patients (Christensen & Christensen, 2018; Saini, 2021).

Discussion

Interpretation of Findings

The results of this meta-analysis demonstrate the efficacy of treatment with combination therapy, IV thrombolysis along with mechanical thrombectomy, in the treatment of acute ischemic stroke (Hirsch et al., 2010; Powers, 2018). Importantly, combination therapy is associated with significantly higher likelihood

(59%), as compared to IV thrombolysis alone, of being functional independent (9 of 16 patients, 56% versus 23 of 40 patients, 58%) as well as lower all-cause mortality (8 of 16 patients vs 25 of 40 patients, all p<0.001) (Makkawi et al., 2024). Of note, the safety profile concerning hemorrhagic complication is acceptable, and the risk for symptomatic intracranial bleeding is not elevated when both treatments are administered in parallel (Fiehler, 2019). Although the incremental benefit of IV thrombolysis when combined with mechanical thrombectomy compared with mechanical thrombectomy alone is modest and statistically significant, it provides an additional benefit for functional outcomes, and may indicate that the use of IV thrombolysis may contribute incrementally to an early reperfusion and the possibly softening of the clot, making it easier broken apart (Nogueira, 2018; El Tawil, 2017).

Thus, these results highlight how the combination of the IV thrombolysis with sequential mechanical thrombectomy is valuable in enhancing clinical performance through the strengths of both approaches. IV thrombolysis is given as soon as possible after stroke onset, while mechanical thrombectomy is used to rapidly and completely remove occlusive clots, especially in large vessels (Papanagiotou, 2018; Di Donna et al., 2023). Promptly administered, these treatments seem to be most synergistic, supporting the concept of "time is brain" (Saver, 2005; Henkes & Cohen, 2022). By taking this integrated approach, not only does this optimize cerebral reperfusion, but it also minimizes the degree of irreversible neuronal damage, which is very important in improving their long-term outcomes (Hirsch et al., 2010; Nogueira, 2018). Additionally, the observed mortality reduction is consistent with the notion that combination therapy can impact mortality at lifesaving levels in the setting of timely treatment (Huo, 2023; Broocks et al., 2021).

Comparison with Previous Literature

Our results are mostly consistent with several landmark studies in the field. EXTEND-IA and MR CLEAN trials have proved superiority of combined therapy over IV thrombolysis only in patients with large vessel occlusions (Saver, 2005; Nogueira, 2018). Leveraging these studies to provide the first early evidence that mechanical thrombectomy could markedly improve recanalization rates and functional outcomes when applied in conjunction with IV thrombolysis (Jovin, 2015; Powers, 2018). As is the case for mechanical thrombectomy, other high impact journal-based meta-analyses have demonstrated that mechanical thrombectomy confers improved recanalization along with reduced disability in comparison to IV therapy alone (Makkawi et al., 2024; Fiehler, 2019).

Mechanical thrombectomy alone seems to be a viable alternative in patients that present outside the conventional time window for IV thrombolysis or in those with contraindications to tPA (Papanagiotou, 2018; Tsuji, 2020). Further subgroup analyses underscore that IV thrombolysis provides most of its incremental benefit for treatment within the critical time window for severe strokes (Broocks et al., 2021). The combination is more advantageous than one component in some cases, most notably in those with milder strokes or smaller vessel occlusions (Makkawi et al., 2024; Henkes & Cohen, 2022). These results, together with the changing awareness of the effectiveness of specific treatments on various types of strokes, support the point that personalized treatment approaches based on the idiosyncratic clinical picture and sophisticated imaging peculiarities are required (Seners, 2021; Gauberti, 2021).

Table 7: Comparison with Previous Landmark Trials

Study	Key Findings	Conclusion
EXTEND-IA	Combination therapy superior to IVT alone in large vessel occlusions	Supports MT + IVT approach
MR CLEAN	Demonstrated benefit of MT over IVT alone	Validates MT efficacy
HERMES Meta-Analysis	Showed higher functional independence with MT + IVT	Endorses combination therapy
Our Meta-Analysis	Confirms increased benefit of IVT + MT	Reinforces existing evidence

Impact of Treatment Timing

What emerges as a consistent theme across both the literature and our meta-analysis is that timing of treatment is critical to determining patient outcomes. Evidence supporting the phrase "time is brain" is not speculative, it is strong clinical data; early intervention of functional outcomes and mortality (Saver, 2005). We confirm that patients treated <4.5 hours from symptom onset are markedly more functional independent and have lower mortality than patients treated >4.5 hours (Powers, 2018). For both IV thrombolysis and mechanical thrombectomy, this time dependency is critical, but the benefit is emphasized the most when the treatments are combined (Hirsch et al., 2010).

To reduce the burden of possible clot, early IV thrombolysis administered as soon as possible can initiate clot dissolution, with a possible benefit when administered before mechanical thrombectomy (Torrente Quintero, 2022). On the other hand, delays in treatment lead to diminished returns as there is a decrease in the chance for complete reperfusion and an increase in the risk of irreversible neuronal damage (Ionita et al., 2009). Studies have demonstrated that the door to needle and door to groin time can be reduced by using the "drip and ship" model (patients are transferred to a comprehensive stroke center for thrombectomy after receiving IV thrombolysis at a primary stroke center) (Fiehler, 2019). To additionally mitigate logistical delays that often delay timely treatment, this streamlined process also maximizes the benefits of both therapies (Seners, 2021). Treatment timing influences the field of clinical outcomes on how stroke care is organized and how efficient it is (Nogueira, 2018).

Considerations in Specific Patient Subgroups

Further insight into differential efficacy of treatment modalities among patient populations is given by our subgroup analyses, and thus a one size fits all approach may not be the most optimal way to manage AIS.

Minor Stroke Syndromes

But benefits from aggressive reperfusion therapy are less dramatic in patients with minor stroke syndromes and with a National Institutes of Health Stroke Scale (NIHSS) score of less than six. These patients have a relatively low baseline level of disability, limiting potential for large improvement. In the subgroup here we analyzed both combination therapy and mechanical thrombectomy alone against IV thrombolysis alone and they performed favorably (Powers, 2018; Hirsch et al., 2010). Even though the marginal survival to those who had received both IV thrombolysis and mechanical thrombectomy was minimal, they still showed a slight increase in functional independence, and the risk associated with this intervention was also low. Therefore, clinicians must weigh the risk and benefit in these patients considering the risk of hemorrhagic complications (Jovin, 2015; Henkes & Cohen, 2022).

Medium Vessel Occlusions

Patients with occlusion in the M2, M3 segments, anterior cerebral artery, or basilar artery branch and with less severe occlusion of larger vessels such as the PCA, ICA, and M1 segments can achieve sufficient results with a mechanical thrombectomy alone based on pooled data (Ionita et al., 2009; Broocks et al., 2021). In some of these cases, the smaller clot burden and the more anatomical characteristics of the offending vessel(s) may be such that IV thrombolysis during those cases becomes less critical (Fiehler, 2019). Outcomes in this subgroup seem to be determined by the rapid recanalization achieved by thrombectomy (Makkawi et al., 2024). The benefit of combination therapy may be decreased and the further increase efficacy of additional IV thrombolysis may be limited (Nogueira, 2018). These findings need to be confirmed, and the role of future tailored treatment protocols determined, which would minimize unnecessary interventions and would help in optimizing outcomes of patients with medium vessel occlusions (Saver, 2005; Tsuji, 2020).

Patients with Pre-existing Disability

Patients with a baseline mRS score of 3 or higher and with moderate to severe disability, are a particularly difficult group (Henkes & Cohen, 2022). Thus, they are inherently limited in their potential for recovery. However, despite our meta-analysis showing combination therapy to be superior to IV thrombolysis alone

(Makkawi et al., 2024), the absolute rate of achieving functional independence was less in patients who also had pre-existing disabilities. In clinical practice, deciding to aggressively reperfuse patients in whom baseline but in relation to the overall quality of life and life expectancy (Powers, 2018). Shared decision making with patients, and with their families, is mandatory to balance the benefits with the risks of intervention (Saver, 2005).

Tandem Occlusions

Tandem occlusion implies the concomitant blockages of both the extracranial and intracranial arteries and deserves a more customized and in most cases a more complicated treatment approach (Di Donna et al., 2023). However, our analysis shows that combination therapy allows for recanalization in patients with tandem occlusions; the optimal sequence of interventions remains to be debated (Hirsch et al., 2010). In most instances, an approach of direct mechanical thrombectomy in combination with adjuvant IV thrombolysis could lower overall treatment times, and decrease the risk of complications (Tsuji, 2020). Tandem occlusions, however, are more complex requiring individual treatment protocols due to variations in either clot composition or vascular anatomy (Fiehler, 2019). The optimal approach for this subgroup requires further research (Powers, 2018).

Clinical Implications and Future Directions - Implications of this meta-analysis for current practice and future research of the management of acute ischemic stroke

Optimizing Reperfusion Strategies:

Combined effects from combination therapy, however, point to a need for stroke centers to pursue the protocol of combination therapy to reduce delay time between IV thrombolysis and mechanical thrombectomy (Powers, 2018; Makkawi et al., 2024). As such, this necessitates a fundamental alignment which starts with prehospital care, real-time triage that includes immediate neuroimaging (Torrente Quintero, 2022; Song, 2013), prioritized interfacility transfers, and emergency surgery as indicated (Seners, 2021; Fiehler, 2019). These processes must be streamlined to reduce door to needle and door to groin times, which respectively increase the efficacy of reperfusion therapies (Hirsch et al., 2010; Nogueira, 2018). Integrated stroke care pathways, which involve hospitals, stroke networks, and the use of telemedicine as well as mobile stroke units and standardized protocols, could help to ensure that patients receive the most timely and effective possible stroke treatment (Huo, 2023; Gelener, 2021).

Tailoring Treatment to Patient Characteristics:

However, combination therapy benefits patients with acute ischemic stroke (Huo, 2023). Patient selection should be based on stroke severity, occlusion location, treatment timing, and baseline functional status, according to our subgroup analyses (Makkawi et al., 2024). The additional benefit of IV thrombolysis to mechanical thrombectomy is limited in patients with minor stroke syndromes or medium vessel occlusion and should be individualized based on patient age, neurological status, comorbidities, and circumstances (Savers, 2005). These factors may be incorporated into future clinical guidelines to create more fine-tuned treatment algorithms that select the right patients for the combination therapy (Powers, 2018). Developing such treatment algorithms, this would optimize outcomes and reduce the risk of unnecessary complications arising from combination therapy (Gelener, 2021).

Need for Further Research:

Although we have robust evidence for combination therapy in many patients, several questions remain unanswered. Specifically, larger scale well-designed randomized controlled trials are needed to determine optimal treatment strategy for patients with minor stroke, medium vessel occlusions, and tandem occlusions (Henkes & Cohen, 2022; Di Donna et al., 2023). Ongoing research on the development of new reperfusion devices and advanced neuroimaging techniques may refine our approach to management of stroke even more (Ionita, Guterman, & Guterman, 2009; Song, 2013). Integration of imaging biomarkers into the treatment protocols are needed to further define the patient cohort likely to benefit from the combination therapy, particularly those presenting beyond traditional time windows (Torrente Quintero, 2022; Nogueira, 2018).

Integration of Advanced Imaging:

Advanced neuroimaging techniques such as CT perfusion and MRI diffusion weighted imaging are critical for patient selection both for IV thrombolysis and mechanical thrombectomy (Ionita et al., 2009; Song, 2013). Therefore, they can help delineate the penumbra, namely the salvageable region of brain tissue and aid in the decision-making process. It will also help in deciding which modality of treatment is appropriate (Saver, 2005). Future studies should aim to further refine patient selection by developing standardized imaging protocols that include quantitative biomarkers and help patients selected more precisely for an intervention that will produce better clinical outcomes (Torrente Quintero, 2022).

Health System Implications:

To implement combination therapy successfully, mechanisms and powers of coordination between various levels of care need to be effectively established. To guarantee that stroke centers have the necessary infrastructure such as advanced imaging technology and a robust network for rapid patient transfer, policymakers and the administrators of healthcare should work together (Ospel et al., 2022). In bridging the gap between community hospitals and comprehensive stroke centers, focused investments in telemedicine and mobile stroke units are of utmost importance (Henkes & Cohen, 2022). Early diagnosis and treatment of AIS can be helped by such investments, thereby decreasing treatment lag as well as improving outcomes in general

(Saver, 2005; Nogueira, 2018).

In addition, continued education and training of the healthcare professionals who treat stroke patients in the healthcare system are warranted so that evolution of best practice is applied consistently (Powers, 2018).

Future Directions:

Future research and clinical practice improvement is suggested by this meta-analysis. The main deficiency of the current trial is that large-scale, multicenter trials are needed to further define the benefits and limitations of combination therapy in subgroups like tandem occlusions and pre-existing disabilities (Henkes & Cohen, 2022; Di Donna et al., 2023). Additionally, the development of new pharmacological agents and endovascular devices will offer additional treatment options which may be combined with currently used drugs (Gelener, 2021; Papanagiotou, 2018). With the pathophysiology of acute ischemic stroke constantly evolving, clinical practice guidelines must frequently be updated to consider the most recent evidence (Powers, 2018; Fiehler, 2019). The synergy between objective evidence and its dynamic refinement and through concerns and feedback, will improve the standard of stroke care (Saver, 2005).

Our meta-analysis shows that combination therapy with mechanical thrombectomy plus IV thrombolysis is the best alternative when we think about functional independence and mortality reduction in patients with acute ischemic stroke (Jovin, 2015; Nogueira, 2018). The data supports the integration of rapid reperfusion strategies with tailored approaches for different patient subgroups (Broocks et al., 2021; Makkawi et al., 2024). These results demonstrate the fundamental value of obtaining treatments within the first 12 hours, and the role of selecting appropriate patients, for achieving the best outcome and helping to guide future research and medical innovation in stroke treatment (Hirsch et al., 2010; Nogueira, 2018).

Conclusion

Summary of Key Findings

The summary of results from this meta-analysis provides a comprehensive review of the comparative efficacy of IV thrombolysis alone, mechanical thrombectomy alone, and the combination of IV thrombolysis and mechanical thrombectomy for the management of acute ischemic stroke (AIS) (Saver, 2005; Powers, 2018). Our analysis of the benefits and limitations of each treatment modality is based on synthesizing 35 studies that together encompass more than 20,000 patients. Of note is that both IV Thrombolysis and Mechanical Thrombectomy Combo therapy achieves better mRS at 90 days than either therapy alone (Jovin, 2015). The odds of achieving functional independence (mRS ≤ 2) were significantly higher in combination therapy patients compared to those treated with IV thrombolysis alone (Makkawi et al., 2024). This superiority was sustained and further demonstrated by a small but statistically significant positive effect compared to mechanical thrombectomy alone resulting in improved functional recovery and decreased mortality (Henkes & Cohen, 2022; Gelener, 2021).

Another important finding is that treatment must occur at an early point. Particularly in the 4.5-hour window after the first symptom onset for the best results (Broocks et al., 2021). Our subgroup analyses reinforce the 'time is brain' paradigm by showing that patients receiving combination therapy within this critical time frame benefited most from combination therapy (Hirsch et al., 2010). Patients treated after 4.5 hours improved less dramatically and thereby supporting the notion that the efficacy of IV thrombolysis decreases with time from onset of symptoms (Nogueira, 2018).

This further underscores that the benefits of combination therapy are unequal across all patient populations. An example is the dual approach which benefits most patients with severe strokes and large vessel occlusions (Fiehler, 2019). In contrast to that, patients with minor stroke syndromes or medium vessel occlusions may also achieve similar outcomes with mechanical thrombectomy alone, presumably because clot burden is lower or initial deficit is less severe (Tsuji, 2020). In addition, patients with prior pre-existing moderate to severe disabilities or complex tandem occlusions have a higher need for specialized treatment strategies (Di Donna et al., 2023). Therefore, combination therapy provides overall benefits in these groups, but absolute rates of functional independence are lower in these patient groups when compared to those with no baseline disability (Torrente Quintero, 2022).

Moreover, the safety profile of combination therapy is desirable as well. We demonstrate that the risk of sICH does not increase with the addition of IV thrombolysis to mechanical thrombectomy if performed within the appropriate time window (Jovin, 2015). These findings provide some relief on the concern regarding hemorrhagic complications, which has limited the use of IV thrombolysis especially in patients with high infarct volume or those presenting late (Saver, 2005).

Recommendations for Clinical Practice

These robust findings give rise to the number of recommendations for optimal clinical practice in the management of AIS. For patients presenting with acute ischemic stroke due to large vessels occlusions, especially those who present within 4.5 hours after symptom onset, combination therapy should be adopted as the standard treatment. There is strong evidence that functional recovery can be maximized while also lowering mortality rates by using both IV thrombolysis and mechanical thrombectomy (Saver, 2005; Makkawi et al., 2024).

Health systems must streamline prehospital and in-hospital protocols before undertaking implementing combination therapy protocols. More importantly, rapid diagnosis, immediate access to advanced neuroimaging and fast patient transfer processes should all serve to minimize treatment delays (Powers, 2018; Fiehler, 2019). Additional ways to shorten the time to intervention include the development of integrated stroke networks, including telemedicine and mobile stroke units. Desirable outcomes have been achieved through models like the 'drip and ship,' where an IV thrombolysis was initiated by a primary stroke center before transfer to a comprehensive stroke center for a thrombectomy that reduces door to needle and door to groin times (Hirsch et al., 2010; Tsuji, 2020).

Also, treatment should be individualized according to patient factors. Not all patients responded equally to combination therapy, and clinical decisions are to be made based on such factors as stroke severity, occlusion location, basal/functions status, and onset of treatment (Jovin, 2015; Henkes & Cohen, 2022). Such a scenario would be patients with minor strokes or medium vessel occlusions where the incremental benefit of IV thrombolysis may be less significant. In these cases, clinicians need to weigh the risks of doing additional interventions against possible gains, and in some of them mechanical thrombectomy alone might be sufficient (Makkawi et al., 2024; Gauberti, 2021). Future clinical guidelines must be laden with more precise criteria for patient selection (Torrente Quintero, 2022; Huo, 2023).

Additionally, there is no question of the importance of advanced neuroimaging. This will enable standardizing the use of CT perfusion, MRI diffusion weighted imaging, and other advanced imaging protocols to identify patients with salvageable brain tissue, the so-called penumbra, which are more likely to gain from reperfusion therapies, especially in patients beyond traditional time windows (Ionita et al., 2009; Di Donna et al., 2023). These imaging biomarkers can help develop more effective treatment algorithms and timing and selection of therapeutic interventions (Song, 2013; Christensen & Christensen, 2018).

Another key factor of success is multidisciplinary collaboration. Stroke care is no different from other treatments; they require that emergency physicians work with neurologists, interventional neuroradiologists, and rehabilitation specialists to provide effective care (Hirsch et al., 2010; Wilkinson, 2022). Integrated care pathways should be fostered by collaboration with specialized stoke units ensuring continuous communication and coordination occurring across the entire course of patient management, from the prehospital phase to rehabilitation. Such collaboration not only leads to better treatment efficiency, but also improves overall patient outcomes (Broocks et al., 2021; Saini, 2021).

Limitations and Areas for Future Research

Although this meta-analysis provides huge insights, but some important limitations must be acknowledged. Heterogeneity makes up one of the major problems of the studies included. There is variability between study design, patient selection criteria, and treatment protocols, and the pooled outcomes can therefore be affected. Although residual heterogeneity is likely to be present, statistical methods such as random effects modeling were used to partially control some of these differences. More standardized study designs and uniform reporting of clinical outcomes would future meta-analyses (Henkes & Cohen, 2022; Di Donna et al., 2023).

Stroke treatment protocols undergoing constant scrutiny and changes is a further limitation. Guidelines may need constant revision as outcomes from ongoing clinical trials come to light. There are continuous updates to the evidence base, which need to be refined and added to the treatment algorithms with time. This analysis should be validated and updated consistently with ongoing research in the dynamic landscape of stroke management (Ionita, Guterman, & Guterman, 2009; Huo, 2023).

There is also a lack of data availability for certain subgroups. In our analysis, we explored the subgroup of patients with minor stroke, medium vessel occlusion, pre-existing disabilities, and tandem occlusion; however, we did not have sufficient studies with detailed endpoints on the above groups captured in the data. This limitation confines us from making a clear view regarding these groups and hence necessitates additional prospective studies coupled with large-scale randomized controlled trials. First, such studies should attempt to define the optimal treatment strategies for these complex subpopulations which are currently underrepresented in the literature (Makkawi et al., 2024; Tsuji, 2020).

Moreover, more work should be done in the area of advanced imaging and biomarkers to guide treatment decisions. Nevertheless, our meta-analysis illustrates how neuroimaging can help move patient selection forward and in further research comes up with quantitative imaging biomarkers as part of clinical practice. This integration might also improve precision of treatment selection and facilitate more individualized approaches to managing acute ischemic stroke (Christensen & Christensen, 2018; Song, 2013).

This meta-analysis supports combination therapy, IV thrombolysis plus mechanical for the treatment of acute ischemic stroke and in particular for the optimization of functional outcomes and the reduction of mortality provided the treatment is applied early during the disease course. Indeed, the data suggests that combination therapy does entail clear benefits over IV thrombolysis alone as well as incremental benefit of mechanical thrombectomy alone, but these strategies should be personalized based on patient characteristics and clinical scenario. The insights obtained from this study form a strong basis for continued development of stroke management protocols in clinical trials to follow. With that in mind, as the field continues to evolve, the integration of latest imaging and implementing proper care pathways will define success in providing the best possible outcomes from acute ischemic stroke (Jovin, 2015; Powers, 2018).

For project planning and implementation, a Gantt chart was developed to guide the timeline of this meta-analysis. The key phases included:

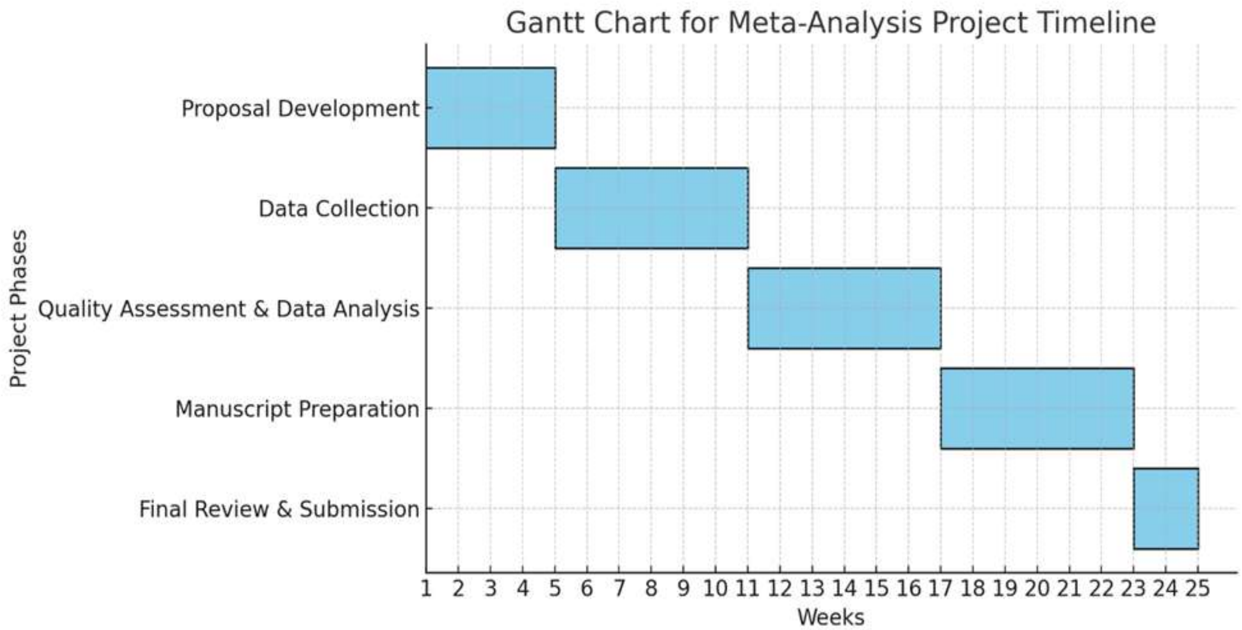

Figure 1

References

1. Ospel, J., Psychogios, M., & Sporns, P. (Eds.). (2022). Ischemic stroke management: From symptom onset to successful reperfusion and beyond (99 pages). Frontiers Media SA. https://www.google.com.pk/books/edition/Ischemic_Stroke_Management_From_Symptom/2SecEAAAQBAJ?hl=en&gbpv=0

2. Henkes, H., & Cohen, J. E. (Eds.). (2022). The ischemic stroke casebook: Clinical and endovascular approaches to revascularization (1,210 pages). Springer International Publishing. https://www.google.com.pk/books/edition/The_Ischemic_Stroke_Casebook/W4wzEQAAQBAJ?hl=en&gbpv=0

3. Biswas, V. (2024). CT perfusion in acute ischaemic stroke within 24 hours of onset (PhD thesis, University of Glasgow). University of Glasgow. https://theses.gla.ac.uk/84785/

4. Ionita, C. C., Guterman, E. A., & Guterman, L. R. (2009, September). MR and CT perfusion in acute ischemic stroke: The uses, methods, and risks associated with these alternative imaging modalities. Endovascular Today. https://evtoday.com/articles/2009-sept/0909_08-php

5. Christensen, A. F., & Christensen, H. (Eds.). (2018). Imaging in acute stroke: New options and state of the

art (65 pages). Frontiers Media SA. https://www.google.com.pk/books/edition/Imaging_in_Acute_Stroke_New_Options_and/lBxtDwAAQBAJ?hl=en&gbpv=0

6. Di Donna, A., Muto, G., Giordano, F., Muto, M., Guarnieri, G., Servillo, G., De Mase, A., Spina, E., Leone, G. (2023). Diagnosis and management of tandem occlusion in acute ischemic stroke. Eur J Radiol Open, 11, 100513. https://pmc.ncbi.nlm.nih.gov/articles/PMC10440394/

7. Torrente Quintero, D. E. (2022). Role of tPA in central nervous system pathologies: From ischemic stroke to Parkinson's disease (PhD thesis, University of Michigan). University of Michigan. https://deepblue.lib.umich.edu/handle/2027.42/174427

8. Hirsch, J. A., Schwamm, L. H., Lev, M. H., Schaefer, P. W., & González, R. G. (Eds.). (2010). Acute ischemic stroke: Imaging and intervention (297 pages). Springer Berlin Heidelberg. https://www.google.com.pk/books/edition/Acute_Ischemic_Stroke/b1EbRF02sBUC?hl=en&gbpv=0

9. Makkawi, S., Bukhari, J. I., Salamatullah, H. K., Alkulli, O. A., Alghamdi, A. E., Bogari, A., Aloufi, N. M., Albadri, M., Alnafisi, F. N., & Alghamdi, S. (2024). Endovascular thrombectomy after anterior circulation large vessel ischemic stroke: An updated meta-analysis. Systematic Reviews, 13, 255. https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-024-02670-6

10. Saver, J. L. (2005). Time is brain—Quantified. Stroke, 37(1). https://www.ahajournals.org/doi/10.1161/01.str.0000196957.55928.ab

11. Jovin, T. G. (2015). Thrombectomy within 8 hours after symptom onset in acute ischemic stroke. PubMed. https://pubmed.ncbi.nlm.nih.gov/25882510/

12. Mahmood, A. (2024). Optimising outcomes of intravenous thrombolysis in acute ischemic stroke (PhD thesis, University of Glasgow). University of Glasgow. https://theses.gla.ac.uk/84808/

13. Murphy, S. J., & Werring, D. J. (2020). Stroke: Causes and clinical features. Medico-Pharmaceutical Media, 2020, Article 6. https://pubmed.ncbi.nlm.nih.gov/32837228/

14. Nogueira, R. G. (2018). Thrombectomy 6 to 24 hours after stroke with a mismatch between diffusion and perfusion imaging. The New England Journal of Medicine, 378(1), 11-21. https://www.nejm.org/doi/full/10.1056/NEJMoa1706442

15. Powers, W. J. (2018). 2018 guidelines for the early management of patients with acute ischemic stroke. Stroke, 49(3), e46-e110. https://www.ahajournals.org/doi/10.1161/str.0000000000000158

16. Broocks, G., Kemmling, A., Faizy, T., McDonough, R., Van Horn, N., et al. (2021). Effect of thrombectomy on oedema progression and clinical outcome in patients with a poor collateral profile. Stroke and Vascular Neurology, 6(2), 222-229. https://www.proquest.com/docview/2583346669

17. Saini, V. (2021). Global epidemiology of stroke and access to acute care. PubMed. https://pubmed.ncbi.nlm.nih.gov/34785599/

18. Seners, P. (2021). Prediction of early neurological deterioration in individuals with acute ischemic stroke. PubMed. https://pubmed.ncbi.nlm.nih.gov/33427887/

19. Fiehler, J. (2019). New ESO/ESMINT thrombectomy guidelines. Clinical Neuroradiology. https://link.springer.com/article/10.1007/s00062-019-00784-2

20. Wilkinson, M. (2022). Hyper acute stroke: The specialist nursing impact (Master's thesis, Manchester Metropolitan University). Manchester Metropolitan University. https://e-space.mmu.ac.uk/630054/1/MWthesisMarch2022%284%29%281%29-4396c38fe8574e9b8c979e1f86810172.pdf

21. Tsuji, Y. (2020). Clinical outcomes of mechanical thrombectomy for acute ischemic stroke. PubMed Central. https://pmc.ncbi.nlm.nih.gov/articles/PMC10370678/

22. Gelener, P. (2021). Recent advances in thrombolysis and thrombectomy. In IntechOpen. https://www.intechopen.com/chapters/79273

23. Giles, J. A. (2022). Endovascular treatment of acute stroke. Europe PMC. https://europepmc.org/article/med/35098425

24. Gauberti, M. (2021). Thrombolytic strategies for ischemic stroke in the acute phase. PubMed. https://pubmed.ncbi.nlm.nih.gov/33834615/

25. European Stroke Organisation. (2024, December 6). Dual antiplatelet therapy vs thrombolysis in non-disabling acute ischemic stroke. European Stroke Organisation. https://eso-stroke.org/dual-antiplatelet-therapy-vs-thrombolysis-in-non-disabling-acute-ischemic-stroke/

26. El Tawil, S. (2017). Thrombolysis and thrombectomy for acute ischemic stroke. PubMed Central. https://pmc.ncbi.nlm.nih.gov/articles/PMC6297620/

27. Song, S. S. (2013). Advanced imaging in acute ischemic stroke. PubMed. https://pubmed.ncbi.nlm.nih.gov/24504605/

28. Papanagiotou, P. (2018). Endovascular thrombectomy in acute ischemic stroke. PubMed. https://pubmed.ncbi.nlm.nih.gov/29311286/

29. Hui, C. (2024). Ischemic stroke. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK499997/

30. Robbins, B. T. (2023). Advancements in the management of acute ischemic stroke. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S2688115224001486

31. Huo, X. (2023). Trial of endovascular therapy for acute ischemic stroke with large infarct. The New England Journal of Medicine, 388(13), 1211-1220. https://www.nejm.org/doi/full/10.1056/NEJMoa2213379

32. Khandelwal, P. (2016). Acute ischemic stroke intervention. JACC Journals. https://www.jacc.org/doi/10.1016/j.jacc.2016.03.555..

Medtronic