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Neuroimaging and Intravenous Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke beyond 4.5 Hours: A Systematic Review

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ABSTRACT

Introduction: Current guidelines suggest giving intravenous recombinant tissue plasminogen activator (rt-PA) within 4.5 hours after acute ischemic stroke onset or the time the patient was last-seen-well. Patients often arrive at the hospital after 4.5 hours, making thrombolysis treatment challenging. It is crucial to examine expanding this timeframe beyond 4.5 hours of onset or last-seen-well. **Objective:** This systematic review intended to examine the effectiveness and safety of IV rt-PA in patients presenting to the hospital beyond 4.5 hours of onset or last-seen-well. **Methods:** We searched PubMed, Scopus, and ScienceDirect for studies on acute ischemic stroke patients treated with IV rt-PA alteplase beyond 4.5 hours of onset or last-seen-well. Outcomes comprised the Modified Rankin Scale (mRS) score, intracranial hemorrhage (ICH), symptomatic ICH, and mortality. We assessed the risk of bias using Cochrane Risk of Bias Vol 2 and ROBINS-I. **Results:** Eleven randomized controlled trials and observational studies were selected. Most subjects were above 65 years, and their baseline mean or median NIHSS scores were 6–12. Seven studies had specific neuroimaging criteria for eligibility, such as DWI/FLAIR or T2WI mismatch, PWI/DWI mismatch, or CT/MR perfusion. In RCTs, alteplase group had 47.1% to 53.3% favourable results (mRS 0-1) compared to 41.3% to 48.3% in placebo/controls group and 23% to 85% in observational studies. Compared to the placebp/control group and onset within 4.5 hours, alteplase typically had better ourcomes. However, ICH, symptomatic ICH, and mortality were numerically higher, albeit not statistically significant. **Conclusion:** IV rt-PA alteplase can be given for up to 9-12 hours from onset or last-seen-well with neuroimaging evidence of salvageable tissue, such as the perfusion imaging RAPID criteria or DWI/FLAIR or T2WI mismatch, taking consideration of hemorrhage and mortality concerns.

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INTRODUCTION

Ischemic stroke is the world's second leading cause of death and disability. It mostly happens in low- and middle-income countries. In 2016, the world reported 13.7 million new stroke cases, with ischemic strokes accounting for 87% of these incidents.[1] Rapid treatment is crucial due to the time-dependent progression of stroke damage.[2] Current guidelines from the American Stroke Association recommend intravenous thrombolysis with recombinant tissue plasminogen activator as the standard treatment for eligible patients, as long as it is given within 4.5 hours of onset or the patient's last-seen-well. This suggested timeframe is grounded in key clinical trials showing the safety and effectiveness of IV rt-PA within this period.[3]

However, many patients attend the hospital beyond the 4.5-hour time window due to delayed symptom recognition, transportation issues, unknown onset, or other reasons. Patients often present after the best timeframe for treatment, with about 1-8% of ischemic stroke patients receiving IV rt-PA therapy.[4] IV rt-PA is usually not given to these patients because the risk of complications, like intracranial hemorrhage, is deemed to exceed the potential benefits.[3] As a result, there is a need for effective treatment options for ischemic stroke patients who present beyond the conventional time window.

New developments in neuroimaging techniques, such as perfusion and magnetic resonance imaging (MRI), have made it possible to identify patients with brain tissue or penumbra that can be saved and treated with endovascular interventions, even if it's already too late.[5,6] This has made people more interested in studying the potential of IV rt-PA administration beyond 4.5 hours after last-seen-well or onset in carefully selected patients using advanced neuroimaging.[7,8] A literature review has been published that presents the most recent clinical trials of IV rt-PA administration beyond 4.5 hours of onset or last-seen-well. In order to obtain new insights into this topic that could improve patient care, we aim to conduct a systematic review of the literature on the use of IV rt-PA beyond the conventional time window.[9]

OBJECTIVE

This review aimed to evaluate the effectiveness and safety of IV rt-PA in acute ischemic stroke patients after a 4.5-hour time window by systematically reviewing the existing literature. By examining the outcomes of the literature, we could provide evidence that might expand the therapy options available to this underserved population and eventually improve patient outcomes.

METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[10]

Eligibility criteria

Original research, such as randomized trials, non-randomized trials, observational studies, and primary studies from any review that the reviewer found, was considered eligible. Data from studies also include the results of the Modified Rankin Scale (mRS) assessment to evaluate its effectiveness, as well as information on intracranial hemorrhage, symptomatic intracranial hemorrhage, and the mortality rate to assess its safety. This study included adults aged 18 and older who had ischemic strokes with an onset time or last-seen-well over 4.5 hours. The intervention evaluated was IV thrombolysis with alteplase; the studies must be full free text or studies that can be accessed by the reviewer and published between 2014 and 2024 in English. Our review only looked at the effects of alteplase intervention. It didn't include studies that looked at other types of strokes, like hemorrhagic or transient ischemic attack, or studies that used IV rt-PA thrombolysis along with endovascular treatment.

Information sources

Studies were identified by searching the PubMed, Scopus, and ScienceDirect databases. Additional search strategies include checking the reference lists of the included studies for citations.

Search strategy, selection, and data collection process

The search terms used on PubMed and Scopus were (*"tissue plasminogen activator" OR "alteplase" OR "rt-PA" OR "rtPA" OR "tPA" OR "tenecteplase" OR "thrombolysis") AND ("ischemic stroke" OR "cerebral infarction" OR "brain ischemia" OR "cerebrovascular accident" OR "stroke ischemic") AND ("delayed treatment" OR "extended window" OR "late treatment" OR "beyond 4.5 hours" OR "time window" OR "onset-to-treatment time" OR "4.5 hours")*. However, because ScienceDirect only allowed a maximum of 9 search terms, the reviewer used different search terms, such as *("alteplase" OR "thrombolysis" OR "tenecteplase") AND ("ischemic stroke" OR "cerebral infarction" OR "stroke ischemic") AND ("delayed treatment" OR "extended window" OR "4.5 hours").* We planned to conduct a literature review on both tenecteplase and alteplase interventions. However, upon completing the search,

the reviewer chose to exclude tenecteplase from the study. This decision was made to avoid any potential deviance from the review's primary focus, which is the widely used alteplase thrombolysis. The search engine's default settings were used for this purpose.

The reviewer began by screening titles and abstracts to identify studies for potential inclusion using the Covidence tool. Studies that met the inclusion criteria were then gathered for a thorough full-text review and bias assessment. Following the final selection of studies for inclusion, data extraction was conducted using a template. The template recorded various details such as the authors, publication year, study participants, age and gender, NIHSS scores, treatment window duration, neuroimaging criteria, mRS results, mortality rates, and any incidences of ICH.

Outcome and risk of bias

The modified Rankin Scale (mRS), intracranial hemorrhage (ICH), and mortality rates were the main outcomes evaluated in this study. The severity of the stroke as assessed by the National Institutes of Health Stroke Scale (NIHSS) and baseline patient characteristics (e.g., age and gender) were also examined. The risk of bias in the included studies was assessed using Cochrane Risk of Bias Vol. 2 (ROB-2) and ROBINS-I for randomized trials and non-randomized studies.[11] ROBINS-I and ROB-2 evaluate according to the domain of the specific cause of risk bias. ROBINS-I has seven domains with a judgment of low, moderate, or high risk of bias or no information, while ROB-2 has five domains with a judgment of low, some concerns, and high risk of bias.[11,12]

Data synthesis

The synthesis was based on the results of the included studies, which were chosen following a final review of the full texts. This synthesis focused on the review's major findings and the quality of the studies included.

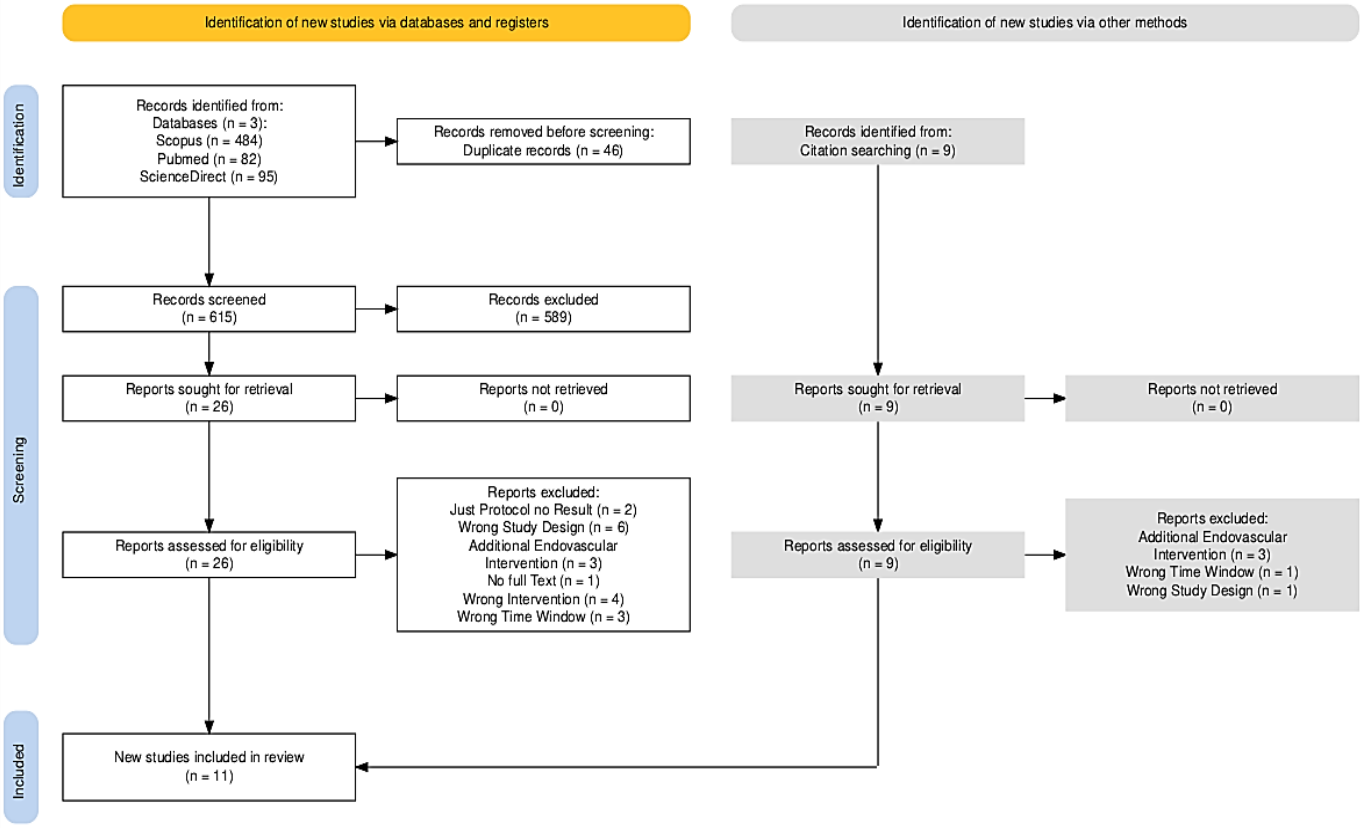

Figure 1. Flow diagram of the included studies

RESULTS

Study selection

A total of 661 studies were gathered from PubMed, Scopus, and ScienceDirect, along with nine studies found through a citation search (Figure 1). The Covidence tool automatically got rid of 46 duplicates, and one reviewer (MRG) read the titles and abstracts of 615 studies before reading the full texts and

assessing the risk of bias by all of the reviewers. Following the identification and screening process, only eleven studies were selected for inclusion (Figure 1). The majority of studies were excluded due to incorrect study design, mixed intervention with endovascular treatment, incorrect intervention, a therapeutic window that did not meet the criteria, and an article that only had a protocol and no results.

Study characteristics

Of the eleven studies, 6 were observational cohort studies, one was a safety trial, and four were randomized trials. All of them used alteplase as an intervention. Table 1 summarizes the study's characteristics and findings.

Alteplase usage

Ten studies used alteplase as an intervention at a normal dose of 0.9 mg/kg, while one study used a low dose of 0.6 mg/kg.[13] The majority of studies have found that the age and other demographic characteristics of ischemic stroke patients are relatively similar, with most of them being elderly or over 65. All studies found that the baseline median or mean score of NIHSS for ischemic stroke patients ranged from 6 to 12, and all of them had a therapeutic time window that extended beyond 4.5 hours last-seen-well. However, two studies required that a patient initiate treatment within 4.5 hours of onset.[13,14] the upper limit varied among studies, with some allowing for 6 hours[15], 9 hours[7,16,17], or even 12 hours.[18,19]

Based on the favorable outcome of mRS (0-1) after 90 days of the randomized controlled trial, the effectivity in the alteplase group ranged from 47.1% to 53.3%, while the placebo/control group ranged from 41.3% to 48.3%. Two studies employed DWI/FLAIR mismatch, one used PWI/DWI mismatch, and the other used the CT/MR perfusion.

In observational studies, the treatment's effectiveness as measured by mRS (0-1) ranged from 23% to 85%. Another study compared severity instead of effectivity using mRS (3-6).[17] A study by Schwamm *et al*. without a control group revealed 38.8% of patients had an mRS score of 0-1 at 90 days.[14] Gumbinger *et al.* found that thrombolysis administered beyond 4.5 hours of onset produced favorable outcomes compared to no treatment. The modified Rankin Scale (mRS) outcomes were looked at in three studies, with symptom onset occurring within and beyond 4.5 hours of onset or last-seen-well.[15,17,19] These studies showed similar efficacy between the onsets, as measured by mRS (0-1) at 90 days. Another study by Cortijo *et al.* compared the percentage of mRS (0-1) between beyond 4.5 hours of witnessed onset and beyond 4.5 hours of last seen well unknown onset at 90 days, also showing relatively similar results, which are 45.9% and 31.2%, respectively.[20] The neuroimaging criteria varied from study to study, which included CT perfusion, MR perfusion, DWI/FLAIR mismatch, and DWI/T2WI mismatch. Four studies did not specify neuroimaging criteria.

Most of the studies showed that the IV rt-PA group beyond 4.5 hours of onset or last-seen-well had higher rates of ICH/SICH and mortality compared to either the placebo/control group or the group with time within 4.5 hours of onset. The range for mortality was from below 1% to 26%, while the range for symptomatic intracranial hemorrhage (SICH) ranged from 1% to 17.2%. However, the differences were not statistically significant. The only exceptions were one study that found a higher prevalence of parenchymal hematoma (PH) type 2 in the alteplase group beyond 4.5 hours of onset or last-seen-well,[8] and another study that found the incident of SICH more frequently within 4.5 hours of onset than beyond 4.5 hours of onset.[17] Full information on the individual studies is presented in Table 1.

Table 1. Summary of the included studies

Author, year	Study Subject	Study Design	Study Characteristic Baseline	Window Period	Neuroimaging Requirement	Effectiveness	Safety
Gumbinger et al. 2014[18]	- Total: 84,439 subjects. - 74,176 subjects did not receive rt-PA therapy. - 10,263 subjects received rt-PA therapy. - 721 were at an onset of more than 4.5 hours.	Retrospective cohort	- **Mean age**: the average age was 73.5 years overall, 73.7 years for the group that did not receive rt-PA, and 72.7 years for those who did. - **Gender**: males made up 51% of the group that didn't receive rt-PA and 53.5% of the group that did receive rt-PA. - **NIHSS**: patients receiving rt-PA had a mean score of 10.2, whereas those not receiving it had a score of 6.	4.5 up to 12 hours	- Mismatch CT (computer tomography) or MRI (magnetic resonance imaging) neuroimaging (not specified). - Neuroimaging was used in 43% of patients treated beyond 4.5 hours of onset.	- mRS (0–1) at discharge (10 days) in patients with onset beyond 4.5 hours rt-PA: 23.9%. - In selected patients, rt-PA treatment beyond 4.5 hours was associated with a higher likelihood of a favorable outcome (modified Rankin Scale score 0-1) compared to no treatment. The adjusted odds ratio was 1.25 (95% CI: 1.01 to 1.55).	- Mortality: 81 (11.2%). - The adjusted odds ratio for mortality with rt-PA treatment beyond 4.5 hours was 1.45 (95% CI: 1.08 to 1.92), indicating a higher mortality risk compared to no rt-PA treatment.
Thomalla et al. 2018[8] (WAKE UP)	- Total: 503 subjects. - Alteplase group: 254 subjects. - Placebo group: 249 subjects.	Multicenter, randomized, double-masked, placebo-controlled clinical trial.	- **Mean age**: 65.3 ± 11.2 years in the alteplase group, meanwhile patients in the placebo group were 65.2 ± 11.9 years old. - **Gender**: 65% were male in the alteplase group and 64.3% in the placebo group. - **NIHSS**: median score in the alteplase and	Unknown onset or last-seen-well was beyond 4.5 hours	The MRI DWI/FLAIR (Diffusion Weighted Imaging/Fluid Attenuated Inversion Recovery) showed a mismatch, with an abnormal signal on DWI but no hyperintense signal on FLAIR	- mRS (0–1) at 90 days 53.3% in the alteplase group 41.8% in the placebo group. - The main outcome of the study showed a significant positive odds ratio of 1.61 (95% CI 1.09 to 2.36, p =	- Mortality at 90 days in the alteplase group compared to the placebo group was 4.1% vs. 1.2%, adjusted odds ratio 3.38 (95% CI 0.92-12.52, p = 0.07). - SICH) (NINDS): Alteplase: 20 Placebo: 12

			placebo group were 6.			0.02), indicating that alteplase outperformed the placebo in achieving a favorable outcome (modified Ranking Scale score of 0 or 1) at 90 days	(p = 0.13) (8% vs. 4%) - Parenchymal hematoma type 2 was more prevalent in the alteplase group than placebo (4.0% vs. 0.4%; adjusted odds ratio 10.46, 95% CI 1.32-82.77, p = 0.03).
Schwamm et al. 2018[14] (MR WITNESS)	Total: 80 subjects	Prospective, open-label, multicenter, and safety trial.	- **Mean age**: 67.5 ± 13.5 years old. - **Gender**: male with a percentage of 53%. - **NIHSS**: mean score was 7.	- Last-seen-well 4.5 to 24 hours. - Treatable with alteplase within 4.5 hours of onset.	- qDFM refers minimal or no hyperintensity on FLAIR imaging, which is in accordance with restricted diffusion on DWI. The minimum threshold for FLAIR hyperintensity is specified as a signal intensity ratio of less than 1.15.	- mRS (0–1) at 90 days: 38.8% Median score at 90 days was 2.	- SICH: 1 (1.3%) - Symptomatic edema: 3 (3.8%) - AICH: 2 (26.6%) - Mortality: 7 (8.8%)
Bai et al. 2019[19]	- Total: 601 subjects. - 274 subjects within 4.5 to 12 hours of onset. - 327 subjects within 4.5 hours of onset.	Retrospective study	- **Mean age**: in the 4.5 - 12 hours onset group, 59.17 ± 8.59 years, and in the 4.5 hours onset group, 59.25 ± 9.46 years. - **Gender**: 68% were in the 4.5 hours onset group, while 66.18% in	4.5 - 12 hours of onset.	MRI DWI changes but no change in T2WI or FLAIR.	- mRS (0–1) at 90 days: Patients in the 4.5–12 hours onset group accounted for 85.04%. Patients who had onset within 4.5	- AICH: 13 (4.74%) in the 4.5 - 12 hours of onset group and 13 (3.98%) in the within 4.5 hours of onset group. - SICH: 3 (1.09%)

			the 4.5 - 12 hours onset group. - **NIHSS**: mean score was 10.98 ± 4.10.			hours accounted for 86.85%. - At 90 days, the functional outcome of mRS 0-1 was not statistically different between groups (p = 0.679).	in the 4.5 - 12 hours of onset group and 3 (0.92%) in within the 4.5 hours of onset group (p = 0.526). - Mortality: 2 (0.72%) occurred in the 4.5 hours group and 2 (0.73%) in the 4.5-12 hours group (p = 0.583).
Ringleb et al. 2019[16] (ECASS-4)	- Total: 119 subjects - 60 rtPA subjects (2 patients could not be evaluated for 90-day mRS. - 56 placebo subjects (1 patient could not be evaluated for 90-day mRS).	Randomized, multicenter, double-masked, placebo-controlled phase 3 trial.	- **Median age:** 78 years. - **Gender:** 56.3% male. - **NIHSS:** mean score was 10.6.	The onset or wake-up stroke occurs within 4.5–9 hours, with the mean occuring between the last time the patient was seen well and the onset of symptoms.	MRI PWI (Perfusion-weighted imaging: DWI mismatch ratio of 1.2 and minimum PWI volume of at least 20 ml.	- mRS (0–1) at 90 days: 35% in rt-PA group. 28.6% in the placebo group. - At 90 days, favoring the alteplase (rt-PA) group over the placebo group was not statistically significant (odds ratio 1.346, 95% CI 0.613-2.954, p = 0.4585).	- SICH: 1 (1.6%) in rt-PA group. - Mortality did not significantly differ between the placebo and control group at 90 days (11.5% and 6.8%, respectively; p = 0.53). - Hemorrhagic Transformation: 7 (11.5%) in the rt-PA group and 3 (5.2%) in the placebo group (p = 0.3238)

Ma et al. 2019[7] (EXTEND)	- Total: 225 subjects - 113 subjects alteplase group - 112 subjects placebo group	Multicenter, randomized, placebo-controlled	- **Mean age:** 73.7 ± 12.7 years in the alteplase group and 71.0 ± 12.7 years in the placebo group. - **Gender:** 52.2% male in the alteplase group and 58.9% in the placebo group. - **NIHSS:** median score was 12 in the alteplase group and 10.0 in the placebo group.	Between 4.5 and 9.0 hours after onset or awakening, sleep onset unkwnown	- **CT & MRI Rapid software:** ischemic core mismatch ratio of > 1.2 between the hypoperfusion volume and the irreversible volume, a volume difference of more than 10 ml, and an irreversible tissue volume of less than 70 ml. - **TTP (Time to Peak)** >6s: hypoperfused - **CBF (Cerebral Blood Flow)** < 30%: irreversible tissue or use MRI DWI.	- mRS (0–1) at 90 days: 35.4% in alteplase group. 29.5% in the placebo group. • Adjusted risk ratio of 1.44 (95% CI 1.01-2.06, p = 0.04) for the primary outcome, favoring the alteplase (IV thrombolysis) group over the placebo.	- SICH: 7 (6.2%) in the alteplase group and 1 (0.9%) in the placebo group (adjusted risk ratio 7.22, 95% CI 0.97-53.54, (p = 0.053). - Mortality was numerically higher with alteplase at 90 days (11.5%) compared to placebo (8.9%), but this difference was not statistically significant (adjusted risk ratio 1.17, 95% CI 0.57-2.40, p = 0.67).
Cortijo et al. 2014[20]	- Beyond 4.5 hours witnessed onset: 37 subjects - Beyond 4.5 hours last-seen-well unknown onset: 32 subjects	Prospective study	- **Mean age:** Beyond 4.5 hours witnessed onset: 68.6 ± 12.9 years Beyond 4.5 hours Last-seen-well unknown onset: 75.4 ± 10.7 years - **Gender:** female. Beyond 4.5 hours witnessed onset: 51.47% Beyond 4.5 hours last-seen-well unknown onset:43.8%	- Beyond 4.5 hours from onset or last-seen-well	- The infarct core CBV did not surpass one-third of the MCA territory, and the tissue is considered at risk when the MTT–CBV mismatch exceeds 20%. - An infarct core was defined as a region on the CBV map with a value	- mRS (0–1) at 90 days: Beyond 4.5 hours witnessed onset: 45.9% Beyond 4.5 hours Last-seen-well unknown onset: 31.2% (p = 0.212)	- PH type 2: Beyond 4.5 hours witnessed onset: 3.1% Beyond 4.5 hours Last-seen-well unknown onset: 2.7% - Hemorrhagic transformation:

			NIHSS: median score was 10 in the witnessed onset group and 12 in unknown onset group.		of less than 2 ml/100 g. Brain tissue at risk was defined as having MTT > 145% on the contralateral side and a CBV > 2.0 ml/100 g in the same territory.		Beyond 4.5 hours witnessed onset: 3.1% Beyond 4.5 hours Last-seen-well unknown onset: 2.7%
Koga et al. 2020[13] (THAWS)	- Total: 131 subjects - 70 subjects alteplase group 61 subjects placebo group	Investigator-initiated, multicenter, randomized, open-label, blinded-end point evaluation, controlled trial	- **Mean age:** 73.2 ± 12.4 years in the alteplase group and 75.8 ± 11.9 years in the control group. - **Gender:** males made up 74% in the alteplase group and 51% in the control group. - **NIHSS:** median score was 7 in both groups.	- Stroke symptoms during waking hours or with an unknown onset, if the onset is more than 4.5 hours ago, are well-know and treatable within 4.5 hours of dicovery.	- Mismatch between the presence of an abnormal signal on DWI and the absence of a signal change (negative FLAIR pattern) in the corresponding ischemic region. - Negative FLAIR	- mRS (0–1) at 90 days: 47% in the alteplase group 48.3% in the control group - No significant difference in outcome of mRS 0-1 at 90 days (alteplase 47.1% vs. control 48.3%, RR 0.97, 95% CI 0.73-1.30, (p = 0.892)	- SICH: 1 (1.4%) in the alteplase group (RR infinity, 95% CI 0.06 to infinity, p > 0.999). Mortality: 2 (2.8%) in the alteplase group and 2 (3.3%) in the control group (RR 0.85, 95% CI 0.06-12.58, (p > 0.999)
Altersberger et al. 2023[17]	- 0–4.5 hours: 15,164 subjects - > 4.5–9 hours: 553 subjects	Cohort prospective	- **Mean age:** 73 years old in both groups. - **Gender:** males made up in both groups, 55% and 54%, respectively. - **NIHSS:** median score was 8 in both groups.	Onset >4.5–9 hours or last-seen-well.	- Advanced neuroimaging: CT perfusion, MR perfusion, MR diffusion-weigtened imaging (DWI) with fluid attenuated inversion recovery (FLAIR) - Non-advanced neuroimaging: non-contrast CT	- mRS (3–6) at 90 days: 0–4.5 hours: 40.4% > 4.5–9 hours: 41.8% (p = 0.482)	- SICH: 0–4.5 hours: 4.3% > 4.5–9 hours: 3.9% (p = 0.678) - Mortality: 0–4.5 hours: 12.6% > 4.5–9 hours: 12.8%

					and/or CT angiography only - Advanced imaging and MR perfusion significantly reduce mortality in cases with onset beyond 4.5 hours (p = 0.027, p = 0.037)		(p = 0.884)
Wang et al. 2015[15]	- 0–4.5 hours of onset: 194 subjects - > 4.5–6 hours of onset: 29 subjects	- Restrospective cohort	- **Mean age:** 0–4.5 hours: 64.4±10.0 years > 4.5–6 hours: 66.8±9.2 years - **Gender:** 0–4.5 hours: 60% male > 4.5–6 hours: 75% male - **NIHSS:** median score was 7 in both groups.	4.5–6 hours of onset	Not available	- mRS (0–1) at 90 days: 0–4.5 hours of onset: 53.1% ➢ 4.5–6 hours of onset: 51.7% (p = 0.8905)	- SICH: 0–4.5 hours of onset: 10.8% > 4.5–6 hours of onset: 17.2% (p = 0.3153) - Mortality: 0–4.5 hours of onset: 5.2% > 4.5–6 hours of onset: 6.9% (p = 0.5010)
Huang et al. 2019[21]	- Onset to treatment (OTT) 0–90 minute: 5 subjects - OTT 91–180 minute: 38 subjects - OTT 181–270 minute: 37 subjects - ≥ 270 minute: 15 subjects	Restrospective cohort	- **Median age:** OTT 0–90 minute: 69 years old OTT 91–180 minute: 65 years old OTT 181–270 minute: 62 years old OTT ≥ 271 minute: 66 years old - **Gender:** OTT 0–90 minute: 80% male OTT 91–180 minute:	More than 4.5 hours of onset or last-seen-well	Not specified	- mRS (0–1) at 90 days: OTT 0–90 minute: 100% OTT 91–180 minute: 71.% OTT 181–270 minute: 67.6% OTT ≥ 271 minute: 73.3%	- SICH: 4.2% in the total population - Mortality: 8.4% in the total population

	78.9% male OTT 181–270 minute: 64.9% male OTT ≥ 271 minute: 53.3% male **Median NIHSS:** OTT 0–90 minute: 13 OTT 91–180 minute: 5 OTT 181–270 minute: 8 OTT ≥ 271 minute: 6

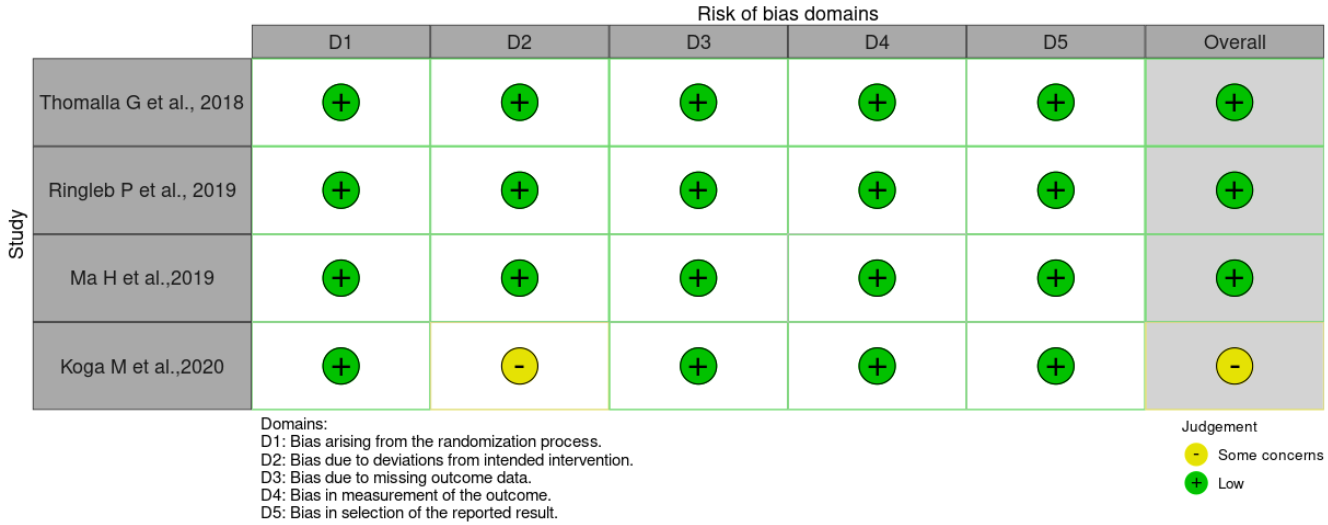

Figure 2. Risk of bias in randomized studies

Figure 3. Risk of bias in non-randomized studies

Risk of Bias

Figures 2 and 3 summarize the risk of bias assessment results. We classified 25% of the randomized trials as having moderate risk of bias due to specific imbalances in baseline characteristics caused by open-label settings, which led to certain deviations in the bias of intended interventions; the remaining 75% were classified as having a low risk of bias. There was a moderate risk of bias in 42% of the non-randomized studies because of uncontrolled confounding factors. There may also be a risk of selection bias in the retrospective study design. The majority of the studies did not state whether the outcome assessors were aware of the intervention or not. The other 58% were classified as low-risk, with only a moderate risk of bias in confounding factors.

DISCUSSION

This review examined the literature on IV rt-PA in ischemic strokes beyond 4.5 hours of onset or last-seen-well. This review identified 36% of the studies as having a moderate risk of bias. The remaining 64% were classified as having a low risk of bias. The key outcomes of this review are effectiveness and safety. Seven of the studies we looked at met certain neuroimaging criteria for IV thrombolysis rt-PA beyond 4.5 hours of onset or last-seen-well. As a result, we tried to focus our discussion on the neuroimaging criteria.

DWI/FLAIR or T2WI mismatch

Four studies found that the DWI/FLAIR mismatch, characterized by an abnormal signal on DWI but no hyperintense signal on FLAIR, was effective. Thomalla *et al*. found that the alteplase group ouperformed the placebo group.[8] Another study by Schwamm *et al*. showed that IV rt-PA was safe for more than 4.5 hours after last-seen-well and continued to work well for up to 24 hours.[14] But in that study, treatment had to begin within 4.5 hours of symptom recognition, and the minimum threshold for FLAIR hyperintensity was set at a signal intensity ratio of less than 1.15. However, it looks like IV rt-PA's effectiveness, as shown by mRS (0-1), changes depending on the dose given after 4.5 hours of onset or last-seen-well. Koga *et al*. did a study and found no significant difference in favorable outcomes between the alteplase low dose of 0.6 mg/kg and the control group beyond 4.5 hours last-seen-well.[13] Still, the favorable outcome is comparable with Thomalla *et al*., the result of 47% in the intervention group.[8] This suggests that a regular dose of 0.9 mg/kg is still more preferable.

A study by Bai *et al*. found that alteplase can be given at a normal dose for up to 12 hours of onset or last-seen-well, as long as the MRI DWI changes but not the T2WI or FLAIR.[19] The results showed that there was no significant difference in favorable outcomes between starting treatment beyond 4.5 to 12 hours of onset compared to those administered within

4.5 hours of onset. This result demonstrated that DWI/T2WI or FLAIR mismatch remains effective beyond 4.5 hours of onset for up to 12 hours, exhibiting efficacy comparable to that within 4.5 hours. This study also reported the highest percentage of mRS (0-1) at 90 days, which was 85%. This is likely similar to the DWI/FLAIR mismatch, but further research is necessary to determine which is better. Adil *et al*. showed the feasibility of adapting FLAIR negative in clinical practice, which is expected to increase the utilization of rt-PA.[22] All of this suggests that IV rt-PA with DWI/FLAIR or T2WI mismatch is effective beyond 4.5 hours last-seen-well or onset with a regular dose of alteplase 0.9 mg/kg for up to 12 hours.

Perfusion Imaging RAPID criteria

Ma *et al*. did a study using software to process neuroimaging. They used a CT/MR perfusion mismatch ratio of > 1.2 between hypoperfusion volume and the irreversible volume, which means that there was a difference in volume of more than 10 ml and an irreversible tissue volume of less than 70 ml with TTP > 6s. This was used to define hypoperfused tissue, and CBF < 30% or MRI DWI, was used to define infarct core or irreversible tissue.[7] The result demonstrated a significant difference in favorable outcomes, favoring the alteplase group over the placebo group. This means the neuroimaging criteria by Ma *et al*., are effective for IV rt-PA beyond 4.5 hours of onset or last-seen-well with CT/MR perfusion for up to 9 hours with normal dose alteplase. Cortijo *et al*. also conducted a study using CT perfusion imaging criteria, achieving a similar favorable outcome of 31% to 45% between witnessed and unwitnessed onset beyond 4.5 hours of onset.[20] However, due to the complexity of the neuroimaging criteria and the lack of a randomization, we decided not to recommend the neuroimaging criteria used in their study in this discussion

PWI/DWI mismatch

Ringleb *et al*. demonstrated the effectiveness of PWI/DWI, a mismatch ratio of 1.2, and a minimum PWI volume of at least 20 ml.[16] There were no significant differences in favorable outcomes between the alteplase and placebo groups, suggesting it may not be as effective as other neuroimaging criteria. Furthermore, the lack of statistical power in this study could potentially lead to a statistical error, as the study explicitly stated that the sample size was insufficient to achieve 80% statistical power.

According to a study by Gumbinger *et al*., patients who received IV rt-PA after 4.5 hours and up to 12 hours had a better chance of a favorable outcome than those who did not receive IV rt-PA. Also, 43% of the patients who received treatment after 4.5 hours used the neuroimaging mismatch paradigm.[18] Altersberger *et al*. also discovered that advanced neuroimaging, which includes CT perfusion, MR perfusion, and MR diffusion-weighted imaging (DWI) with fluid-attenuated inversion recovery (FLAIR), significantly reduces mortality when the onset occurs beyond 4.5 hours. They also found no significant difference in the severity of SICH and mRS at 90 days when the onset occurs beyond 4.5 to 9 hours and within 4.5 hours.[17]

We also discovered that neuroimaging criteria may not be necessary for IV rt-PA. A study by Wang *et al*. compared IV rt-PA onset beyond 4.5 hours to 6 hours to onset within 4.5 hours without neuroimaging criteria and found no significant difference in favorable outcome. This suggests that IV rt-PA onset beyond 4.5 hours to 6 hours is comparable in favorable outcome to onset within 4.5 hours.[15] These findings are in line with a study by Huang *et al.*, that showed no large numerical difference in favorable outcome between onset within 4.5 hours to beyond 4.5 hours.[21] However, it did not specify the neuroimaging criteria and upper limit.

Safety of IV rt-PA beyond 4.5 hours

As shown in the results section, the alteplase group had higher rates of SICH/ICH and mortality with onset beyond 4.5 hours compared to the control/placebo or within 4.5 hours group. However, this difference is not statistically significant. A study by Gumbinger *et al*. supports this idea by showing that IV rt-PA given beyond 4.5 hours of onset is associated with a higher risk of mortality compared to no IV rt-PA treatment. Further research is required to confirm these findings. It should also be noted that the use of IV rt-PA beyond 4.5 hours also needs to comply with the guideline criteria for administering IV rt-PA.

Our review discovered that administering IV rt-PA beyond 4.5 hours of onset necessitates advanced neuroimaging, as described in some literatures. We found no evidence in the literature supporting the use of plain CT scans with ASPECT scores as a criterion for patients to receive IV rt-PA beyond 4.5 hours of onset. Therefore, hospitals lacking advanced neuroimaging, such as MRI or perfusion imaging, will be unable to implement the findings of this review.

This review contains several limitations. First, the usage of only three search engines may have resulted in the omission of relevant studies on the topic. Second, the variety of study designs and outcomes makes it challenging to effectively summarize and compare the studies, with comparisons that must be contextualized within the study design. Third, some research shows questionable results due to unknown

statistical power, which may lead to statistical errors.[7,13,16] Fourth, the review protocol was not registered on PROSPERO. Fifth, it is important to emphasize that this review focuses exclusively on alteplase as the thrombolytic agent of interest.

CONCLUSIONS

In conclusion, ischemic stroke patients who are beyond 4.5 hours of onset or last-seen-well can get a normal dose of IV rt-PA, as long as they meet the perfusion imaging RAPID criteria for tissue, DWI/FLAIR, or T2WI mismatch. This treatment can be administered for up to 9 or even 12 hours; careful consideration is necessary, as there is still a risk of hemorrhage and mortality for each patient.

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Conflict of Interest
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