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Systemic Thrombolysis by Alteplase for Acute Ischemic Stroke

Rapid Review with Expert Input

CADTH

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Table of Contents

List of Tables

List of Figures

Abbreviations

AE	adverse event
AIS	acute ischemic stroke
ECASS III	Third European Cooperative Acute Stroke Study
CI	confidence interval
IST-3	Third International Stroke Trial
MA	meta-analysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke study
PRISMS	Potential of rtPA for Ischemic Strokes with Mild Symptoms
RCT	randomized controlled trial
sICH	symptomatic intracranial hemorrhage
TESPI	Thrombolysis in Elderly Stroke Patients in Italy
tPA	tissue plasminogen activator

Key Messages

- Evidence was summarized to determine the effect of alteplase in adult stroke patients.
- There is substantial uncertainty concerning the evidence due to the risk of bias in the available studies and imprecision in how the magnitude of the treatment effects were estimated.
- The identified research suggests that alteplase administered within 3 hours of a stroke might result in:
  - fewer deaths after 18 months and little-to-no difference in death after 7 days, 3 months, 6 months, or 3 years
  - increased brain bleeds after 7 days but no difference after 36 hours or after 3 months
  - improvements in functioning and independence after 7 days and after 6 months; at 3 months, some studies showed no difference in independence and another study showed higher functioning.
- The identified research suggests that alteplase administered between 3 hours and 4.5 hours after a stroke might result in:
  - little-to-no difference in deaths after 3 months; at 7 days, some evidence showed little-to-no difference in death while other evidence suggested more deaths
  - little-to-no differences in brain bleeds after 36 hours; at 7 days, some evidence showed no effect on brain bleeds, while other evidence showed more brain bleeds
  - no differences in functioning and independence after 6 months; at 3 months, some evidence showed no effect on functioning, while other evidence reported improved functioning.

Context and Policy Issues

An ischemic stroke is caused by decreased or blocked blood flow to the brain, which can lead to tissue damage or loss of brain function.[1,2] Stroke affects thousands of individuals in Canada each year, and the number who had an ischemic stroke in 2019 was 524,129.[3] To treat acute ischemic stroke (AIS), alteplase, a tissue plasminogen activator (tPA), is administered as the first line of therapy to dissolve blood clots.[4,5] Alteplase (Activase, Cathflo Activase, and Actilyse[6,7]) is a tPA like tenecteplase, reteplase, and duteplase[8,9]; however, it is the only tPA approved for systemic thrombolysis for AIS patients in Canada.[10]

The Canadian Stroke Best Practice Recommendations for acute stroke management[10] published in 2018 recommend providing alteplase within 4.5 hours of stroke; this guidance applies to acute stroke treatment prehospital and in the emergency department and acute inpatient stroke care settings. In the US, clinical policy by the American College of Emergency Physicians[11] published in 2015 provides recommendations for physicians who work in the emergency department. This guidance[11] recommends that select patients may be administered alteplase within 3 hours after stroke onset, although there is the potential for increased risk of hemorrhage. Further, this guidance recommends that carefully selected patients may be administered alteplase between 3 hours and 4.5 hours of stroke onset despite the known risk of hemorrhage and unknown degree of functional outcome benefit.[11] Guidelines from the American Heart Association and American Stroke Association[12] published in 2019 for prehospital care providers, allied health professionals, physicians, and

hospital administrators recommend that selected patients may be treated within 3 hours and between 3 hours and 4.5 hours of stroke onset and provide different patient criteria for each time window. For example, for the within 3-hour window, alteplase is "recommended" for mild disabling stroke; for the 3-hour to 4.5-hour window, alteplase "may be reasonable" for mild disabling stroke.[12]

A Cochrane systematic review (SR) published in 2014[13] was used as 1 source of evidence for the previously mentioned guidelines. This SR included a summary of the literature on thrombolysis for AIS; earlier stroke trials were found to have imbalances in baseline patient characteristics between study groups, whereas later trials used modern randomization methods to better balance patient characteristics between treatment arms. The imbalance in baseline patient characteristics in these trials prompted the re-analyses of the findings of some trials. In 2020, Alper et al.[14] published an article that re-analyzed the results from 1 trial. In the same year, the *Canadian Journal of Emergency Medicine* published a debate series that presented 2 perspectives regarding the use of alteplase for AIS.[15] Because the Canadian and American guidelines were published between 2015 and 2019, they do not include any evidence on alteplase used for AIS made available since the guidelines were published.

The purpose of this Rapid Review is to summarize the evidence regarding the safety and effectiveness of alteplase administered within 3 hours and alteplase administered between 3 hours and 4.5 hours in adult patients with AIS.

Research Questions

1. What is the clinical effectiveness of systemic thrombolysis by alteplase in patients with acute ischemic stroke if administered within 3 hours of symptom onset?
2. What is the clinical effectiveness of systemic thrombolysis by alteplase in patients with acute ischemic stroke if administered between 3 hours and 4.5 hours from symptom onset?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were alteplase and ischemic stroke. CADTH-developed search filters were applied to limit retrieval to health technology assessments, SRs, meta-analyses (MAs), or network meta-analyses (NMAs), or randomized controlled trials (RCTs) or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014, and January 19, 2022.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Primary studies or trials that were captured in eligible SRs were summarized based on the information available in the SR(s).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were duplicate publications. Studies were also excluded if they were about other recombinant tPAs that were not alteplase, compared different doses of alteplase, compared alteplase administered at different times, gave treatment to patients with unknown timing of stroke onset, or were about the effectiveness of co-therapies included with alteplase.

Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs.

Critical Appraisal of Individual Studies

The methodological quality of included publications was critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[16] for SRs, and the Downs and Black checklist[17] for RCTs. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 737 citations were identified in the literature search. Following screening of titles and abstracts, 674 citations were excluded and 63 potentially relevant reports from the electronic search were retrieved for full-text review. Zero potentially relevant publications

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with acute ischemic stroke
Intervention	Q1: IV alteplase administered within 3 hours from onset of symptoms Q2: IV alteplase administered between 3 hours and 4.5 hours from onset of symptoms
Comparator	Q1 and Q2: Usual care alone without alteplase, placebo
Outcomes	Q1 and Q2: Clinical effectiveness (e.g., neurologic outcomes, symptom-free status, disability-free status), safety (e.g., all-cause mortality, adverse events, bleeding, intracranial hemorrhage, symptomatic intracranial hemorrhage)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials

were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 55 publications were excluded for various reasons, and 8 publications met the inclusion criteria and were included in this report. These comprised 3 SRs[13,18,19] and 3 RCTs; 1 of these RCTs was reported in 3 publications.[14,20-23] Appendix 1 presents the PRISMA[24] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

The scope of all 3 SRs[13,18,19] was broader than the topic of the current review. All SRs included primary studies in which alteplase treatment was administered within 3 hours, between 3 hours and 4.5 hours, and after 4.5 hours (this time point was outside the scope of the current review). One Cochrane SR by Wardlaw et al.[13] also included studies of different thrombolytic drugs administered at different doses. Only the characteristics and results of the subset of relevant studies will be described in this report.

The Lorenzo et al.[22] publication reported on the Thrombolysis in Elderly Stroke Patients in Italy (TESPI) trial results and included an MA that pooled effects from other stroke trials with TESPI trial results. However, because this MA was not based on a systematic search it was not eligible for this Rapid Review; the Lorenzo et al.[22] citation is also included as a reference of potential interest in Appendix 6 with other MAs without systematic searches.

Study Design

The 3 SRs[13,18,19] were published between 2014 and 2020. The Cochrane SR by Wardlaw et al.[13] included results from the following trials: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A, ATLANTIS B, the European Cooperative Acute Stroke Study (ECASS) II, ECASS III, and the National Institute of Neurological Disorders and Stroke (NINDS). The SR by Chen et al.[18] included results from the ATLANTIS A, ECASS II, ECASS III, NINDS and WAKE-UP trials. The Lan et al. SR[19] included results from the NINDS and the Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trials.

The Cochrane SR by Wardlaw et al.[13] included literature published between 1966 and 2013, while the other 2 SRs[18,19] did not specify search dates. One SR with MAs[18] by Chen et al. included 12 RCTs comparing alteplase to placebo in patients treated with alteplase at different time points after stroke onset; 7 of these trials were relevant to this Rapid Review because they provided treatment within 3 hours or between 3 hours and 4.5 hours. The SR by Wardlaw et al.[13] included 27 RCTs in which different tPAs (including alteplase), or placebo were administered after different stroke onset times; 5 trials within this SR were relevant to this Rapid Review because alteplase was provided within 3 hours or between 3 hours to 4.5 hours. The SR by Lan et al.[19] included 7 non-randomized studies and 3 RCTs of which 2 RCTs were relevant to the current report because they compared alteplase to placebo administered within 3 hours or between 3 hours and 4.5 hours. Of the relevant studies included in the SRs, publication dates ranged from 1995 to 2019.

All 3 RCTs were multi-centre studies. One 2021 publication[22] reported on the TESPI RCT.[25] A 2020 publication[14] was a re-analysis of data from the ECASS III RCT,[26] which was conducted because of baseline differences between study groups in the original publication for the trial. This Rapid Review focuses on the re-analysis of the ECASS III trial[14]; however, some study characteristics were obtained from the original article for this trial[26] if not available in the re-analysis report.

Three publications[20,21,23] reported on an RCT, the third International Stroke Trial (IST-3),[27-29] and were published between 2014 and 2016. One publication[23] reported only on mortality at 18-month follow-up; another publication[20] reported only on mortality at 3-year follow-up. A third publication[21] reported on mortality and hemorrhage at 7-day follow-up and on functional outcomes at 6-month follow-up. Some study characteristics were obtained from 3 earlier articles on the IST-3 trial[27-29] if these details were not available in the report of the re-analysis.

Country of Origin

The country of origin of the first author was Scotland for 2 articles,[13,23] China for 2 articles,[18,19] Italy for 1 article,[22] the US for 1 article,[14] Norway for 1 article,[20] and Australia for 1 article.[21] The Chen et al. SR[18] included relevant studies conducted in Australia, China, Europe, and the US. The Lan et al. SR[19] included relevant studies conducted in Australia, Europe, and North America. The Wardlaw et al. Cochrane SR[13] included relevant studies conducted in Australia, Europe, and the US.

The TESPI trial, reported in 1 publication,[22] was conducted at multiple centres in Italy. Another publication[14] reported re-analyzed results for the ECASS III trial,[26] which was conducted at multiple centres across Europe including Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, and the UK. Three articles[20,21,23] reported results from the IST-3 trial,[27-29] which was conducted across the UK, Poland, Italy, Sweden, Norway, Australia, Portugal, Austria, Belgium, Switzerland, Canada, and Mexico. One[20] of these articles only reported results for a subset of patients in the UK, Norway, and Sweden. The IST-3 trial was the only trial in this report that included patients from Canada.

Patient Population

All SRs included adult patients with AIS. In the relevant primary studies from 2 SRs,[18,19] the number of patients ranged from 58 to 730 and their ages ranged from 60 years to 69 years. In the Cochrane SR by Wardlaw et al.,[13] relevant primary studies included all adults or only adults aged 18 years to 80 years.

Across all RCTs,[14,20-23] patients were adults with AIS, and population sizes ranged from 191 to 1,177. The authors did not indicate whether gender or sex were recorded or whether nonbinary identification was recorded, so these results are summarized as reported by the authors of the included studies. In 1 publication[22] with results from the TESPI trial, all patients were older than 80 years, had National Institutes of Health Stroke Scale (NIHSS) scores below 17, and 61.8% were women. In a publication[14] with re-analyzed results from the ECASS III trial, the mean age in the alteplase group was 64.7 years and mean age in the placebo group was 65.6 years. There were 63.2% males in the alteplase group and 57.3% males in the placebo group. In the IST-3 trial,[27-29] which was reported in 3 articles,[20,21,23] of the total population that received treatment within 6 hours of stroke onset, there were 52% females in the alteplase group and 52% females in the standard care group. For those who received treatment within 3 hours, 79.2% were older than 80 years.[21] People who were of child-bearing potential or were breastfeeding were excluded from the IST-3 trial.[27]

Interventions and Comparators

Across all studies, alteplase at a dose of 0.9 mg/kg was administered intravenously within 3 hours of stroke onset or between 3 hours and 4.5 hours of stroke onset. Most studies reported on alteplase administered within 3 hours. One SR,[18] 1 publication[14] on the ECASS III trial, and 2 publications[21,23] on the IST-3 trial reported results for alteplase administered

between 3 hours and 4.5 hours. In the IST-3 trial, which was reported in 3 articles,[20,21,23] alteplase was administered with standard medical care. Comparator groups of included studies were standard care alone (without alteplase) or placebo.

Outcomes

Effectiveness

Effectiveness was measured using different definitions for functional outcomes. Six publications[13,14,18,19,21,22] reported on functional outcomes. These outcomes were measured using the modified Rankin Scale (mRS), the Oxford Handicap Scale, the NIHSS, the Barthel Index, the Glasgow Outcome Scale, or a global outcome. The mRS is a single-item rating to measure functioning after stroke with 6 grades ranging from 0 to 5.[30,31] Grades of 0 or 1 indicate no symptoms or no significant disability; higher grades indicate increasing severity in disability.[30,31] The Oxford Handicap Scale is a derivative of the mRS that uses the same grading and scale but uses the term "disability" versus "handicap."[32] The NIHSS was reported in the results from 1 RCT[14] using an original and modified version. Each version has 15 items with a total score out of 42 in the original version and 46 in the modified version.[14] Each item assesses functioning and is scored 0, 1, 2, 3, or 4 depending on the item.[14] Smaller numbers indicate normal functioning and higher numbers indicate impairment.[14]

The Barthel Index is a 10-item scale measuring a person's ability to function independently.[14,33] The scale ranges from 0 to 100 with higher numbers indicating more independence.[14,33] The Glasgow Outcome Scale is a 5-point scale in which 5 indicates death, 3 indicates severe disability, and 1 indicates independence.[14] The global outcome was reported in the results from 1 RCT[14] as a composite of other individual scales entered into a statistical algorithm that indicated the probability of a favourable outcome.

Safety

Safety outcomes included death reported in all studies,[14,18-23,29] adverse events (AEs) reported in 1 trial,[22] and symptomatic intracranial hemorrhage (sICH) reported in all SRs and 2 RCTs.[13,14,18,19,21,22] In publications on the TESPI and IST-3 trials,[20-23] mortality was referred to as "overall mortality" or from all causes; in 1 publication for the ECASS III trial,[14] it is unclear if mortality was from all causes. One publication from the TESPI trial[22] reported AEs although the definition for general AEs was unclear; for serious AEs, the definition included sICH, cerebral edema, pneumonia, pleuritis, cardiovascular event, pulmonary edema, anemia, cerebrovascular ischemic event, dysphagia, agitation, acute cholecystitis, urinary sepsis, macroscopic hematuria, laterocervical hematoma, femoral fracture after fall, vocal string paralysis, allergic reaction, or fever.

sICH is bleeding inside the skull which affects an individual's neurological state.[13] Intracerebral hemorrhage is a subtype of intracranial hemorrhage in which bleeding occurs in the brain parenchyma.[34] The definition of sICH varied across studies. In some cases, symptomatic intracerebral hemorrhage was also referred to as sICH. Within studies, the terms were also used interchangeably. The term *sICH* will be used in this report to include subtypes in addition to the broader term for all types of ICH that were reported in the included studies.

Definitions of sICH in the TESPI and ECASS III trials[14,22] and in 1 SR[18] were based on the NINDS trials, the ECASS II, or the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). The NINDS definition was any previously unseen sICH with any suspicion of hemorrhage or decline in neurologic status.[35] The ECASS II definition was any sICH in which stroke severity was a change equal to or greater than 4 on the NIHSS.[35] The SITS-MOST

definition of sICH was hemorrhage identified by images obtained 22 hours to 36 hours after treatment localized to parenchymal hematoma type 2 and in which stroke severity was equal to or greater than 4 on the NIHSS.[35] Two SRs[13,19] reported sICH as reported by the authors of included studies. For the IST-3 trial, the definition of sICH was new headache, neurologic deterioration, acute hypertension, vomiting, nausea, or decrease in consciousness.[27]

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Summary of Critical Appraisal

Systematic Reviews

All 3 SRs[13,18,19] stated the populations, interventions, comparators, and outcomes of interest for reviews, and performed an adequately comprehensive search using at least 2 databases. Two SRs[18,19] did not establish a protocol beforehand; the Cochrane SR by Wardlaw et al.[13] had a protocol but did not describe details sufficiently, thus there is a possibility of bias due to selective outcome reporting. In the Wardlaw et al. SR,[13] study screening and extraction was performed in duplicate; however, in the other 2 SRs,[18,19] data extraction was conducted in duplicate, but it is unclear whether screening was done by 2 reviewers so relevant studies may have been missed. Two SRs[13,19] used a satisfactory technique for assessing risk of bias, although it is unclear whether the Chen et al. SR[18] assessed all important items for risk of bias assessment such as confounding, selection bias, and bias in outcome measurement. If all risk of bias considerations were not made, it is unclear whether synthesized evidence may have been from biased studies or if the conclusions align with the quality of the included studies (e.g., it may be overstated). All SRs reported some but not all details about included studies. The Chen et al. SR[18] described populations, interventions, and study designs in sufficient detail, however details about outcomes, follow-up, and sources of funding were not provided for each included study. The Wardlaw et al. SR[13] described interventions, comparators, outcomes, and study designs in sufficient detail, but sources of funding and population sizes were not reported. The Lan et al. SR[19] did not describe populations, comparators, or sources of funding in sufficient detail. This is a limitation since the comparability and applicability of included studies to other primary studies and to the Rapid Review overall was difficult to determine from SR publications alone.

In the Chen et al. SR[18] that reported MA results, the authors used random effects models that incorporated the assumption that studies were measuring different but related intervention effects (i.e., clinical and methodological heterogeneity may exist). This is a strength because this method would have assumed that there was a range of true effects of the intervention.

Two SRs[18,19] declared no conflicts of interest. The Wardlaw et al. Cochrane SR[13] had several potential conflicts of interest including funding, equipment, or recognition from Boehringer Ingelheim, a pharmaceutical company that manufactures alteplase. Further, the authors of this SR were also involved in the conduct or reporting of the trials included in the review itself. It is unclear how this may have affected selection of trials in the SR and interpretation of findings.

Randomized Controlled Trials

The TESPI trial publication[22] had clearly stated objectives, outcomes, patient characteristics, interventions, risk factors, and main findings. Patients were randomized to balance important factors between study groups, which may have influenced outcomes. However, the TESPI trial

was open label with blinded assessment of some but not all outcomes. This is a limitation because knowledge of study assignment may have introduced performance bias (e.g., patients may have been treated differently if clinicians knew what treatment they received). Knowledge of study assignment may have also introduced detection bias, specifically with subjectively measured or self-reported outcomes that were recorded through a telephone interview in this trial.[22,36] The sICH outcome was measured using a change in NIHSS score and imaging scans[25]; bias may have been introduced in the interpretation of these scans and of the NIHSS score because the trial was open label and clinicians interpreting scans were aware of study assignment. The TESPI trial was also terminated early since findings from another study showed that the intervention was favourable, and the authors believed that was no need to continue; the study therefore was underpowered to detect any significant effects since follow-up was not completed. The trial population also included patients older than 80 years with a NIHSS score greater than 17; therefore, results may not be generalizable to other populations.

In the re-analysis of the ECASS III trial publication,[14] authors clearly stated objectives, outcomes, patient characteristics, interventions, risk factors, and main findings. The authors indicated that they specified their analyses beforehand to avoid selective analysis and reporting.[14] Another strength was that the ECASS III trial was conducted across multiple centres, which may have increased generalizability to other populations. Although randomization was conducted in the ECASS III trial to balance important factors between study groups that may have influenced outcomes, the re-analysis was performed to account for baseline imbalance in prognostic variables that were not comparable in the original ECASS III analysis and may have caused selection bias in the original results. The trial[26] was also described as "double blind" and reported blinding of investigators and examiners, although the publication did not specifically state that patients were blinded. It was also unclear whether outcomes were measured objectively or subjectively. Although the re-analysis attempted to correct for issues present in the original data analysis, the secondary investigation of the data may have been limited due to potential bias of the statistician(s)' knowledge of issues in the data; it is unclear whether the re-analysis was conducted in a blinded manner. Further, the authors of the re-analysis publication stated that re-analyses in general cannot definitively create new conclusions and can only increase or decrease certainty in the unadjusted analysis of the original study.[14]

For the IST-3 trial[27-29] reported in 3 publications in this report[20,21,23] there were some strengths and several limitations. Authors of included publications[20,21,23] clearly stated the objectives, main outcomes, patient characteristics, interventions, and main findings. Patients in the trial were randomized to balance important factors between study groups that may have influenced outcomes. Mortality was measured in most cases using complete central death registries for 3 of the countries participating in the study (the UK, Sweden, and Norway), and time was accounted for in survival analyses.

One limitation of the IST-3 trial was that it is unclear if important confounders such as smoking history were measured and thus balanced between study groups. Since the trial was conducted across multiple centres, this may have increased generalizability to other populations; however, because the trial excluded people of child-bearing potential or those who were actively breastfeeding, it is unclear whether results from this large study can be applied to these individuals. The IST-3 trial was open-label so all those involved were aware of study assignment, including outcome assessors. This may have introduced selection, performance, and detection biases. Outside of the UK, Sweden, and Norway, mortality was measured as death reported by physicians, hospital coordinators, or self-reported on

questionnaires or in telephone interviews instead of central death registries. Functional outcomes were also measured through self-reported questionnaires or in telephone interviews. Because the trial was open label, reporting of these outcomes may have been biased. The sICH outcome was measured using a stroke scale or an imaging scale; if only the stroke scale was used, this may have been biased because it was measured using an unblinded outcome assessor's judgment. Authors of the publications[20,21,23] of the IST-3 trial also noted that there was not enough power to detect effects either in the IST-3 trial as a whole or in their individual analyses.

All trial publications[14,20-23] included in this report had potential conflicts of interest. Individuals involved in the conduct of trials or authors of publications of included studies received funds, resources, or recognition from Boehringer Ingelheim, a pharmaceutical company that manufactures alteplase. In addition to this company, authors of IST-3 publications[20,21,23] also received funds, resources, or recognition from various industry sources.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings by time after stroke onset and by outcome, in Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12. The findings summarized in this report are based on the way outcomes are reported in the included publications.

The narrative summaries in this report may contain some data from the same trials because there was overlap in some of trials included within the SRs and in trials between SRs and RCTs. All 3 SRs[13,18,19] included results from the NINDS trials. Two SRs[13,18] included results from the ATLANTIS A, ECASS II, and ECASS III trials. This overlap across SRs is presented in Appendix 5. One included primary study[14] was a re-analysis of the ECASS III trial (conducted by the authors to account for baseline imbalances between study groups), and the findings from the original analysis of the ECASS III (without this adjustment) were included in 2 of the SRs[13,18] summarized in this report.

Clinical Effectiveness of Alteplase Within 3 Hours of Stroke Onset

Mortality

Two SRs[13,18] and 2 RCTs (IST-3[20,21,23] and TESPI trials[22]) reported findings for mortality in patients who received treatment within 3 hours of stroke onset. For death at 7-day follow-up, 1 publication of the open-label IST-3 trial[21] reported little-to-no difference in the odds of death for the alteplase group compared with the usual care group, but the effect estimate was imprecise.

At 3-month follow-up, results from the open-label TESPI trial[22] and MA results from the Chen et al. SR[18] showed little-to-no difference in the risk or odds of death in the alteplase group compared with the control group; however, the effect estimates were imprecise.

At the 6-month follow-up, results from the open-label IST-3 trial[23] suggested little-to-no change in mortality with treatment with alteplase compared with usual care, with substantial imprecision.

At the 18-month follow-up, results from the open-label IST-3 trial[23] reported a reduction in mortality in the alteplase group compared with the usual care group; however, the magnitude of this reduction is uncertain due to imprecision in the results.

At 3-year follow-up, results from the open-label IST-3 trial[20] showed little-to-no difference in mortality in the alteplase group compared with the usual care group; however, these findings were imprecise.

Individual studies in the Wardlaw et al. SR[13] with unknown follow-up times had inconsistent findings. Three RCTs showed little-to-no difference between alteplase and control, but effect estimates were substantially imprecise. One RCT showed a higher odds of death in the alteplase group compared with the control group; however, the magnitude of this increase is uncertain due to the serious imprecision of the results.

Symptomatic Intracranial Hemorrhage

Three SRs[13,18,19] and 2 RCTs (IST-3[21] and TESPI trials[22]) investigated sICH in patients who received treatment within 3 hours of stroke onset. For sICH measured at 36-hour follow-up, MA results from the Chan et al. SR[18] showed little-to-no difference in the odds of sICH in the alteplase group compared with the control group, with substantial imprecision.

For 7-day follow-up, results from the open-label IST-3 trial[21] showed increased odds of sICH in the alteplase group compared with the standard care group; however, the magnitude of the effect is uncertain because of the large imprecision in the results.

For the 3-month follow-up, results from the open-label TESPI trial[22] showed little-to-no difference between the alteplase and standard care groups; however, the findings were affected by serious imprecision.

The Lan et al.[19] and the Wardlaw et al.[13] SRs reported sICH results; follow-up times were not specified in these SRs. Most results from the primary studies in these reviews showed little-to-no difference in sICH when alteplase was compared with control and 1 primary study reported in the Wardlaw et al. SR[13] showed increased odds of sICH in the alteplase group. Results across both SRs[13,19] had a very high level of imprecision.

Functional Outcomes

Three SRs[13,18,19] and 2 RCTs (IST-3[21] and TESPI[22] trials) reported results for functional outcomes in patients who received treatment within 3 hours of stroke onset. For 7-day follow-up, the open-label TESPI trial[22] showed that a statistically significantly higher percentage of patients in the alteplase group had neurologic improvement compared with the standard care group.

For 3-month follow-up, results from the open-label TESPI trial[22] and primary study results from the Lan et al. SR[19] showed little-to-no difference in being alive and independent; these findings were affected by substantial imprecision. The Chen et al. MA[18] showed higher odds of having no symptoms or no significant disability in the alteplase group compared with the control group.

For 6-month follow-up, results from the open-label IST-3 trial[21] showed higher odds of functioning (no symptoms, mild symptoms, or minor handicap) in the alteplase group compared with the standard care group.

For the Wardlaw et al. Cochrane SR,[13] in which follow-up times were not specified, results across individual studies were inconsistent. Findings from 2 primary studies showed little-to-no difference in having favourable outcomes, with large imprecision. Two primary studies showed increased odds of favourable outcomes; these results had a high level of imprecision.

Adverse Events

The open-label TESPI trial[22] that reported results for patients who received treatment within 3 hours showed little-to-no difference between treatment with alteplase and standard care for incidence of AEs and serious AEs.

Clinical Effectiveness of Alteplase Between 3 Hours and 4.5 Hours of Stroke Onset

Mortality

Two SRs[18,19] and results from 2 RCTs (IST-3 trial[21] and the re-analysis[14] of ECASS III results) reported mortality findings in patients who received treatment between 3 hours and 4.5 hours of stroke onset. Seven-day follow-up results from the re-analysis of the ECASS III trial[14] showed little-to-no difference in mortality between treatment with alteplase and placebo, whereas results from the IST-3 trial[21] showed increased odds of death in the alteplase group compared with the standard care group. There was serious imprecision in these findings.

Three-month follow-up results from the Chen et al. MA[18] (which included the original ECASS III trial) and results from the re-analysis of the ECASS III trial[14] both showed little-to-no difference in incidence of death between the alteplase and control groups, but these findings were affected by serious imprecision.

For the Lan et al.[19] SR with unknown follow-up time, results from 1 RCT showed little-to-no difference in incidence of death between the alteplase and control groups; these results had substantial imprecision.

Symptomatic Intracranial Hemorrhage

One SR,[18] results from the IST-3 trial,[21] and re-analysis results from the ECASS III trial[14] reported findings for sICH in patients who received treatment between 3 hours and 4.5 hours of stroke onset. Meta-analysis results from the Chen et al. SR[18] showed little-to-no difference in sICH at 36-hour follow-up; these results had a high level of imprecision.

In the re-analysis of the ECASS trial,[14] authors presented data using different definitions of sICH and different analysis adjustments (i.e., using multivariable effect estimates or stratified effect estimates). For 7-day follow-up, all variations in adjustments showed a higher risk of sICH in the alteplase group compared with the placebo group. Results from the open-label IST-3 trial showed higher odds of sICH in the alteplase group compared with the standard care group; the magnitude of the effect is uncertain because the results had a high level of imprecision.

Functional Outcomes

One SR,[18] results from the open-label IST-3 trial,[21] and re-analysis results from the ECASS III trial[14] reported findings for functional outcomes in patients who received treatment between 3 hours and 4.5 hours of stroke onset. For 3-month follow-up, re-analysis from the ECASS III trial[14] showed little-to-no difference in all functional outcomes for independence and neurologic outcomes, whereas results from an MA by Chen et al.[18] found higher odds of

having no symptoms or no significant symptoms in the alteplase group compared with the control group.

For 6-month follow-up, results from the open-label IST-3 trial[21] showed little-to-no difference in favourable outcomes (having no symptoms, minor symptoms, or minor handicap) in the alteplase group compared with the standard care group.

Adverse Events

No evidence was found that reported on AEs other than death for treatment provided between 3 hours and 4.5 hours after stroke onset.

Limitations

There are several limitations to the evidence that met the criteria for this Rapid Review. The overall quality of the findings was limited by several factors, including a lack of blinding,[20-23] high imprecision of results, uncertainty in whether data were reported correctly based on the interpretation of the findings, differences in trial conduct and analysis among researchers and clinicians, and potential conflicts of interest. Only the IST-3 trial included patients living in Canada so it is unclear whether results from the other studies can be applied to Canada.

There were also differences between the included studies that limited the interpretation of the findings, such as differences in how outcome measures were measured and variations in statistical analyses. It is also unclear whether the evidence base is applicable to younger populations or those of child-bearing potential.

Studies differed in how outcomes were measured, which may make it difficult to compare results. Different definitions of sICH were used, based on previous stroke trials, and some studies reported multiple sICH outcomes based on different definitions. Most studies reported results for functional outcomes based on the mRS or the Oxford Handicap Scale, and the re-analysis of the ECASS III trial[14] reported results based on 5 different scales. Studies also varied in what was considered a favourable outcome; some reported it as complete independence whereas others reported favourable outcome as having some disability but not being completely dependent on others.

Of the evidence that met the criteria for this report, 1 publication, the re-analysis of the ECASS III trial,[14] focused on the safety and effectiveness of alteplase when administered between 3 hours and 4.5 hours of stroke onset. The other primary studies focused on the zero- to 3-hour window,[20,22] or a window of 6 hours or more, and then conducted subgroup analyses for the zero- to 3-hour or the 3-hour to 4.5-hour windows.[21,23] For the Chen et al. SR[18] that conducted MAs and NMAs, the NMA results were not relevant because different time frames were compared to one another, rather than each time frame compared with a control. The Lan et al. SR[19] combined studies with varying treatment windows; therefore, MA results were not relevant to this review. The Wardlaw et al. Cochrane SR[13] conducted MAs; however, these pooled results could not be included in the current report because some studies in the MAs used a dose of alteplase that was not 0.9 mg/kg, included children, or administered a tPA that was not alteplase.

Another limitation of the SRs[13,19] was that the follow-up times were not reported for some of the outcomes, thus these results could not contribute to the narrative summaries for specific follow-up times. Because some SRs did not adequately report details from the original trials, some findings from these trials may be missing in this report.

In addition to the limitations of the evidence on alteplase, there are also limitations within this report. There was overlap in the primary studies in the SRs included in the review which may have resulted in reporting of the results from the same trial in multiple sections of the report. For example, ECASS III trial results were included in the MA from the Chen et al. publication,[18] and the re-analysis of the results from the ECASS III trial were reported in the Alper et al. publication.[14] Furthermore, details from some of the primary studies were not reported in the SRs and thus are not captured in this report. For example, some outcome follow-up times were unclear.

Conclusions and Implications for Decision- or Policy-Making

A Rapid Review was conducted to determine the clinical effectiveness of alteplase for patients with AIS when administered within 3 hours of symptom onset, or between 3 hours and 4.5 hours of symptom onset. Three SRs[13,18,19] and 5 publications[14,20-23] reporting on 3 RCTs were found. Articles were published between 2014 and 2021 and reported effects on mortality, sICH, functional outcomes, or AEs. The SRs included studies in which alteplase was administered at several different time points after stroke onset and included findings from the ATLANTIS A, ATLANTIS B, ECASS II, ECASS III, NINDS, PRISMS, and WAKE-UP trials. One publication[22] reported results from the TESPI trial, in which treatment was administered within 3 hours. Another publication[14] was a re-analysis of results from the ECASS III trial in which treatment was administered between 3 hours and 4.5 hours. Three publications[20,21,23] reported on the IST-3 trial in which treatment was administered within 6 hours; subgroup analyses were reported for the zero- to 3-hour or 3-hour to 4.5-hour windows.

When alteplase was administered within 3 hours of stroke onset, studies showed little-to-no difference on mortality at 7-day,[21] 3-month,[18,22] 6-month,[23] and 3-year follow-ups[20] compared with usual care. For 18-month follow-up, results from an open-label trial[23] showed a reduction in death in the alteplase group compared with standard care. All findings were substantially imprecise, which reduces the overall confidence in the conclusions. Results from an open-label trial[19,22] showed little-to-no difference between treatment with alteplase and standard of care in the incidence of AEs.

Compared with usual care, when alteplase was administered within 3 hours of stroke onset, there was little-to-no difference on sICH after 36 hours based on MA results[18] or at 3 months based on an open-label trial; however, the findings were imprecise.[22] In contrast, 7-day results from an open-label trial[21] showed higher odds of sICH in the alteplase group; however, the magnitude of the effect is unclear due to the imprecision of the results.

When alteplase was administered within 3 hours of stroke onset, there were more neurologic improvements in this group after 7 days compared with standard care based on an open-label trial.[22] After 3 months, findings were inconsistent; results from 3 trials reported in 2 publications[19,22] showed little-to-no difference, whereas 1 MA[18] showed an

increase in favourable outcomes compared with the control group. Results from an open-label trial suggested higher odds for functioning for alteplase compared to standard care after 6 months.

When alteplase was administered between 3 hours and 4.5 hours of stroke onset, a re-analysis of a double-blind trial[14] showed little-to-no difference in mortality after 7 days when compared with placebo, whereas an open-label trial[21] showed increased odds of death after 7 days compared with standard care. Results from 1 MA[18] and a re-analysis of a double-blind trial[14] showed little-to-no difference in mortality at 3 months between alteplase and control groups. The findings were substantially imprecise.

When alteplase was administered between 3 hours and 4.5 hours of stroke onset, 1 MA[18] showed little-to-no difference in sICH between the alteplase and control groups after 36 hours. The findings on sICH for 7-day follow-up were mixed. The re-analysis of a double-blind trial[14] showed little-to-no difference, whereas results from an open-label trial[21] suggested increased risk of sICH with treatment with alteplase compared with standard care; however, the magnitude of the effect was unclear due to the imprecision of the result.

When alteplase was administered between 3 hours to 4.5 hours of stroke onset, 3-month follow-up results were inconsistent when compared with a control group. The re-analysis of a double-blind trial[14] showed little-to-no difference in functional outcomes, whereas results from 1 MA[18] suggested improved functional outcomes. When alteplase was administered between 3 hours and 4.5 hours of stroke onset, an open-label trial[21] showed little-to-no difference in functional outcomes at 6-month follow-up.

There were methodological limitations identified, such as lack of blinding,[20-23]and inconsistencies in how outcomes (e.g., functional outcomes)[13,14,18,19,21,22] were measured and reported. In addition, some authors of included studies declared receiving funds or resources from a pharmaceutical company that manufactures alteplase, were involved in multiple stroke trials, or were authors of review articles that included these trials. Although many analyses found little-to-no difference between groups for the outcomes evaluated, these findings often had substantial imprecision (i.e., wide confidence intervals), and it is possible that this could change with the addition of high-quality, adequately powered studies. Researchers and clinicians may consider investigating whether there is a need to re-analyze data from other trials as was done in 1 included article[14] in which results from the ECASS III trial were re-analyzed due to imbalances across treatment groups. If further work is conducted, it may reduce potential biases that have been identified, such as consideration of potential conflicts of interest of study personnel. New studies could also be conducted in a way that minimizes potential bias by ensuring blinding of all patients and study personnel, investigating imbalances in study groups to increase internal validity, and including personnel and resources not affiliated with pharmaceutical companies. In addition, researchers and clinician groups can discuss how to consistently report on functional outcomes (e.g., what degree of independence is considered favourable) so that studies can be compared to one another. If a gold standard outcome for stroke trials exists, this should be used consistently in future work. If additional work is done in this area, MAs can include new publications to gain a clearer understanding of the role of alteplase in treating AIS.

Overall, the limitations of the literature included in this rapid review[13,14,18-23] and the imprecision of results should be considered when interpreting the findings from this report.

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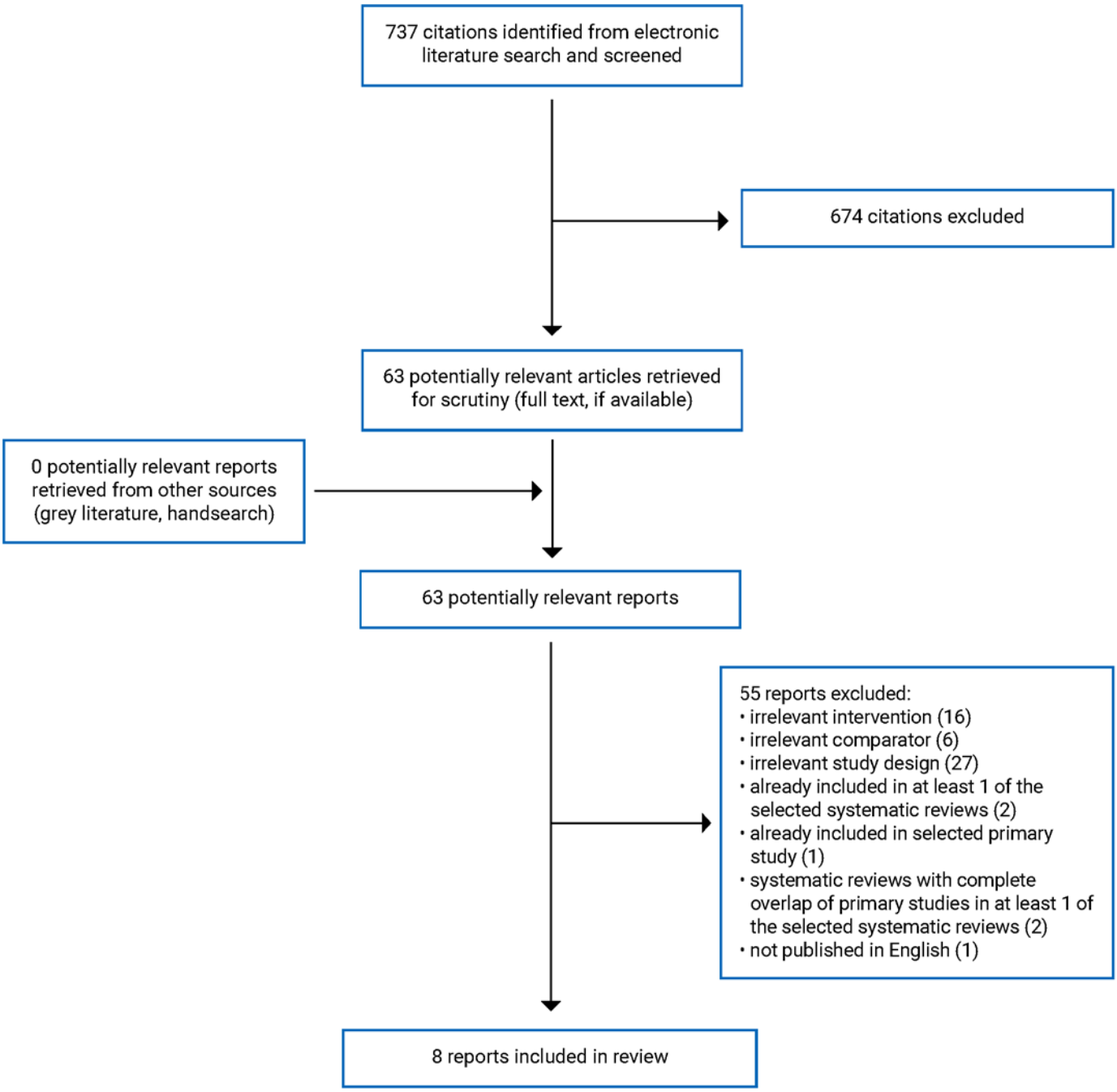
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix was not copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Chen et al. (2020)[18] China Funding: NSFC, NKP of China, Key Project of Department of Science and Technology of Zhejiang Prov., Medical Research Project of Zhejiang Prov.	Publication dates not specified 12 RCTs to conduct MAs and NMAs; MAs of 7 RCTs relevant to current review Includes ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP trials	Patients with AIS 61 to 730 patients with mean age 60 to 69 years	Intervention: IV alteplase 0.9 mg/kg administered within 3 hours, or between 3 to 4.5 hours Comparator: placebo	Outcomes: functional outcomes, sICH, mortality Follow-up: up to 3 months
Lan et al. (2019)[19] China Funding: NSFC, S&T Programs of Guangdong Prov., key point program of Science and Technique plan for production, study, and research of Guangzhou city, S&T Planning Project of Guangdong Prov.	Publication dates not specified 7 NRSs, 3 RCTs; 2 RCTs relevant to current review Includes PRISMS and NINDS trials	Patients with acute minor ischemic stroke (NIHSS ≤ 5) 58 to 313 patients; mean age 62 years in one study and NR in the other	Intervention: IV alteplase 0.9 mg/kg administered within 3 hours Comparator: placebo	Outcomes: functional outcomes, sICH, mortality Follow-up: 3 or 6 months for sICH, unknown for other outcomes
Wardlaw et al. (2014)[13] Scotland Funding: University of Edinburgh, Scottish Office CSO for the Cochrane Stroke Group, Stroke Assoc. and UK MRC, NHS HTA Prog., UK NIHR Cochrane Review Incentive Scheme	Literature searched from 1966 to 2013 27 RCTs; 5 RCTs relevant to current review Includes ATLANTIS A, ATLANTIS B, NINDS, ECASS II, ECASS III, NINDS trials	Patients with definite AIS and without ICH 4 RCTs included patients 18 to 80 years old; 1 RCT included adults of any age	Intervention: IV alteplase 0.9 mg/kg administered within 3 hours Comparator: placebo	Outcomes: functional outcomes, sICH, mortality Follow-up: up to 6 months

AIS = acute ischemic stroke; Assoc. = association; CSO = Chief Scientist's Office; HTA = Health Technology Assessment; IV = IV; MA = meta-analysis; mg/kg = milligrams per kilogram; MRC = Medical Research Council; NIHR = National Institutes of Health Research; NIHSS = National Institutes of Health Stroke Scale; NKP = National Key Research and Development Programme; NMA = network meta-analysis; NR = not reported; NRS = non-randomized study; NSFC = National Natural Science Foundation of China; PAPD = Priority Academic Program Development of Jiangsu Higher Education Institutions; Prog. = program; prov. = province; RCT = randomized controlled trial; S&t = Science and Technology; sICH = symptomatic intracranial hemorrhage or symptomatic intracerebral hemorrhage

Table 3: Characteristics of Included Randomized Controlled Trials

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
TESPI trial				
Lorenzano et al. (2021)[22] Italy Funding: Agenzia Italiana del Farmaco	RCT, multi-centre, open-label	191 patients > 80 years old with AIS who did not have NIHSS score > 17 Mean age 85.1 (SD 3.7), 61.8% women	Intervention (n = 88): IV alteplase 0.9 mg/kg administered within 3 hours Comparator (n = 103): standard care	Outcomes: functional outcomes, sICH, adverse events, all-cause mortality Follow-up: up to 90 days
Re-analysis of ECASS III results				
Alper et al. (2020)[14] US Funding: EBSCO Information Services	Re-analysis of the ECASS III trial which was a multi-centre, double-blind RCT	821 adults with AIS and without ICH, severe stroke, seizure, previous stroke and diabetes, anticoagulant therapy, or surgery or trauma < 3 months Intervention group: mean age 64.7 (SD 12.1), male sex 63.2% Comparator group: mean age 65.6 (SD 11.0), male sex 57.3%	Intervention: IV alteplase 0.9 mg/kg administered between 3 to 4.5 hours Comparator: placebo	Outcomes and follow-up: sICH at 7 days, overall mortality at 7 and 90 days, functional outcomes at 90 days
IST-3 trial				
Berge et al. (2016)[20] Norway Funding: Heart & Stroke Scotland, UK MRC, Health Fdn. UK, Stroke Assoc. UK, Research Council Norway, AFA Insurance, Swedish Heart Lung Fund, Fdn. of Marianne and Marcus Wallenberg, Polish Ministry of Science and Education, Australian Heart Fdn., Australian NHMRC, Swiss National Research Fdn., Swiss Heart Fdn., Assessorato alla Sanita (Regione dell'Umbria, Italy), Danube University	RCT, multi-centre, open-label	Inclusion criteria[27]: clinically definite acute stroke Exclusion criteria[27]: TIA; structural brain lesions; ICH; major trauma, surgery, urinary tract or GI hemorrhage < 21 days; arterial puncture at non-compressible site < 7 days; defect in clotting, coagulation, or platelet function; heparin therapy; person who can give birth or breastfeeding; stroke or thrombolytic therapy < 14 days; dependent in activities of daily living; life-threatening illness; low or high BP; hypo- or hyper-glycemia 613 patients randomized within 3 hours	Intervention: IV alteplase 0.9 mg/kg within 3 hours Comparator: standard care alone	Outcome: all-cause mortality Follow-up: up to 3 years

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Lindley et al. (2015)[21] Australia Funding: same as Berge 2016	RCT, multi-centre, open-label	Criteria: same as Berge 2016 79.2% of patients randomized within 3 hours > 80 years old	Intervention: standard best care plus IV alteplase 0.9 mg/kg administered within 3 hours (n = 431) or between 3 to 4.5 hours (n = 577) Comparator (n = 418 or 600): standard best medical care alone	Outcome and follow-up: sICH within 7 days, all-cause mortality within 7 days, functional outcomes at 6 months
Whiteley et al. (2014)[23] Scotland Funding: same as Berge 2016	RCT, multi-centre, open-label	Criteria: same as Berge 2016	Intervention: standard best care plus IV alteplase 0.9 mg/kg administered within 3 hours (n = 430) or between 3 to 4.5 hours (n = 577) Comparator (n = 418 or 600): standard best medical care alone	Outcome: all-cause mortality Follow-up: up to 18 months

AIS = acute ischemic stroke; BP = blood pressure; EBSCO = Elton Bryson Stephens Company; ECASS III = The Third European Cooperative Acute Stroke Study; fdn. = foundation; GI = gastrointestinal; ICH = intracranial hemorrhage; IQR = interquartile range; IST-3 = third International Stroke Trial; IV = IV; mg/kg = milligrams per kilogram; MRC = Medical Research Council; NHMRC = National Health and Medical Research Council; NIHSS = National Institutes of Health Stroke Scale; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; TESPI = The Thrombolysis in Elderly Stroke Patients in Italy; TIA = transient ischemic attack.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[16]

Strengths	Limitations
Chen et al. (2020)[18]	
Authors clearly stated the population, intervention, comparators, and outcomes of interest. Authors provided justification for only including RCTs. Authors searched at least 2 databases and provided keywords for their search. Authors assessed the quality of studies and performed data extraction in duplicate. For included studies, authors described populations, interventions, and study designs in sufficient detail. Where meta-analyses had high heterogeneity, authors conducted random effects models. Authors assessed the risk of publication bias. Authors declared no conflicts of interest.	It is unclear whether a protocol was established before conducting the review or whether additional sources of relevant literature were searched. It is unclear whether study screening was performed in duplicate. A list of excluded studies with justifications was not provided. Details about outcomes, follow-up, and sources of funding were not provided for each included study. It is unclear if the method to assess the quality of included studies covered all potential risk of bias considerations such as confounding, selection bias, and bias in outcome measurement. It is unclear whether further analyses were conducted to determine the impact of the quality of individual studies on the analyses or overall findings of the review. It is unclear if the sources of heterogeneity were investigated.
Lan et al. (2019)[19]	
Authors clearly stated the population, intervention, comparators, and outcomes of interest. Authors searched at least 2 databases and provided keywords for their search. Authors performed data extraction in duplicate. Authors used a satisfactory technique for assessing the risk of bias of included studies. Authors reported no competing interests.	Details about the review protocol, a list of excluded studies with justifications, an explanation for including all study designs, or the funding of included studies were not provided. It is unclear whether additional sources of relevant literature were searched. It is unclear whether study screening was performed in duplicate. Included studies were not described in adequate detail.

Strengths	Limitations
Wardlaw et al. (2014)[13]	
Authors clearly stated the population, intervention, comparators, and outcomes of interest. Authors provided explanations for study design restrictions. Authors searched at least 2 databases, multiple additional sources, and provided their search strategies. Authors performed study selection and data extraction in duplicate. Authors provided a list of excluded studies with justifications. Authors described the interventions, comparators, outcomes, and study designs of included studies in sufficient detail. Authors used a satisfactory technique for assessing the risk of bias of included studies.	A protocol was established; it is unclear if sufficient detail was provided. Sources of funding and details about population size for each included study were not reported. Authors of the review and of the included studies have received funds, resources, or recognition from Boehringer Ingelheim, a pharmaceutical company that manufactures alteplase. Authors of the review were also involved in the many of the primary studies included in the review.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial

Note that this table has not been copy-edited.

Table 5: Strengths and Limitations of Randomized Controlled Trials Using the Downs and Black Checklist[17]

Strengths	Limitations
TESPI[22]	
Authors clearly stated the objectives, main outcomes, patient characteristics, interventions, risk factors, and main findings. Patients were randomized to study groups.[a] Authors reported random variability in outcomes and exact probability values. Authors reported on adverse events and patients lost to follow-up. Authors described how outcomes were measured.[22]	It is unclear whether the patients recruited, patients prepared to participate, or the staff, places, and facilities where patients were treated were representative of the source population.[a] Patients in the TESPI trial were not blinded, and not all outcome assessors were blinded.[a] sICH measurement included change in NIHSS and imaging scans conducted by assessors who knew study assignment. All other outcomes were measured through a telephone interview which may have introduced detection bias. It is unclear whether statistical tests for the small sample size were appropriate. The trial was terminated early since findings from another study showed the intervention was favourable and there was no need to continue the study. Authors indicated that the study could not detect any statistically significant between-group differences for the main outcome, if any. Patients in the TESPI trial may not be generalizable to patients younger than 80 years old or those with NIHSS scores greater than 17. [a] Not all outcomes were pre-specified beforehand. Five of the authors in the included publication received funds, resources, or recognition from several pharmaceutical or health care companies including Boehringer Ingelheim (manufacturer of alteplase).

Strengths	Limitations
Re-analysis of ECASS III[14]	
Authors clearly stated the objectives, main outcomes, patient characteristics, interventions, confounders, and main findings.[14] The re-analysis plan was specified beforehand to avoid selective reporting of analyses. Patients were randomized to study groups.[b] Authors reported exact probability values. Adverse events and patients lost to follow-up were described. Few patients were lost to follow-up.[b] The study was double-blind. Investigators were not aware of treatment assignments and patients received placebo.[b] Appropriate statistical tests were conducted and described in detail. Important confounders were taken into account in analyses. Patients were recruited from different centres across Europe, which may increase the generalizability of the findings to other European populations.[b] No conflicts of interest were reported for the authors of the re-analysis.	It is unclear whether the patients recruited, patients prepared to participate, or the staff, places, and facilities where patients were treated were representative of the source population.[b] It is unclear if opinions about perceived flaws in the original analyses may have influenced the statisticians who re-analyzed the data. It is unclear if they were blinded. It is unclear whether outcomes were measured objectively or subjectively.[b] The re-analysis is considered hypothesis-generating, new conclusions cannot be drawn with certainty. Authors who conducted the ECASS III trial on which this re-analysis article is based, received funds from Boehringer Ingelheim, a pharmaceutical company that manufactures alteplase.[b]

Strengths	Limitations
IST-3[20,21,23]	
Authors of the included publications clearly stated the objectives, main outcomes, patient characteristics, interventions, and main findings. Authors of the included publications reported exact probability values. In the IST-3 trial, patients were randomized to study groups.[c] In the IST-3 trial, adverse events were measured.[c] In the IST-3 trial, patients were recruited from multiple countries and included older patients and those with more severe stroke, which may increase the generalizability of the findings.[c] In the IST-3 trial, death was determined using central death registries in the UK, Norway, and Sweden in most cases.[c] Authors of the included publications accounted for time in survival analyses. In one publication, the authors noted that their analysis included data of long follow-up time and completeness of data. Missing data for follow-up time was only noted for 1 patient.	In the IST-3 trial, it is unclear whether all important prognostic factors (e.g., smoking status) were considered.[c] In the IST-3 trial, it is unclear whether the patients recruited, patients prepared to participate, or the staff, places, and facilities where patients were treated were representative of the source population.[c] The IST-3 trial included a double-blind phase and then an open-label main study phase where the people involved were aware of treatment assignment. All mortality outcomes measured outside of the UK, Sweden, and Norway were reported by physicians, hospital coordinators, or self-reported on questionnaires or in telephone interviews by people aware of study assignment.[c] In the IST-3 trial, in cases where only the stroke scale was used to determine sICH, this may have been biased since it was measured using an unblinded outcome assessor's judgement.[c] In the IST-3 trial, people who were of child-bearing potential or who were breastfeeding were excluded from the study, limiting generalizability to these populations.[c] In the IST-3 trial, due to the small sample size, it is unclear whether there was statistical power to detect effects.[c] In the Berge et al. publication,[20] 4 of the authors received funds, resources, or recognition from several pharmaceutical or health care companies. In the Lindley et al. publication,[21] 4 of the authors received funds, resources, or recognition from several pharmaceutical or health care companies. In the Whiteley et al. publication,[23] 2 authors received funds, resources, or recognition from Boehringer Ingelheim, a pharmaceutical company that manufactures alteplase.

ECASS III = The Third European Cooperative Acute Stroke Study; IMS = Intercontinental Medical Statistics; IST-3 = third International Stroke Trial; NIHSS = National Institutes of Health Stroke Scale; sICH = symptomatic intracranial hemorrhage; TESPI = The Thrombolysis in Elderly Stroke Patients in Italy.

[a]This critical appraisal point is based on additional trial details obtained from Lorenzo et al. (2012),[25] as these trial details were not reported in the publication included in this report.

[b]This critical appraisal point is based on additional trial details obtained from Hacke et al. (2008),[26] as these trial details were not reported in the publication included in this report.

[c]This critical appraisal point is based on additional trial details obtained from Whiteley et al. (2006),[29] Sandercock et al. (2008),[27] and Sandercock et al. (2012),[28] as these trial details were not reported in the publication included in this report.

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Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix was not copy-edited.

Table 6: Summary of Findings for Alteplase Administered Within 3 Hours of Stroke — Mortality

Study citation and study design	Trial(s)	Effect estimate (CI)	P value
7-day follow-up			
Lindley et al. (2015)[21] RCT	IST-3	OR[a] = 1.43 (99% CI, 0.77 to 2.66)	NR
3-month follow-up			
Lorenzano et al. (2021)[22] RCT[b]	TESPI	RR[c] = 0.69 (95% CI, 0.39 to 1.21)	0.177
Chen et al. (2020)[18] SR Results from MA	ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP and others	OR[c] (pooled) = 0.82 (95% CI, 0.60 to 1.12)	NR
6-month follow-up			
Whiteley et al. (2014)[23] RCT	IST-3	Absolute difference[d] = 3.93% (95% CI, −2.63% to 10.49%)	0.2401
18-month follow-up			
Whiteley et al. (2014)[23] RCT	IST-3	Absolute difference[d] = 7.22% (95% CI, 0.21% to 14.23%)	0.0434
3-year follow-up			
Berge et al. (2016)[20] RCT[e]	IST-3	HR[a] = 0.87 (95% CI, 0.69 to 1.09)	NR
Follow-up time not reported			
Wardlaw et al. (2014)[13] SR Results from 4 RCTs	ECASS II 1998	OR[c] = 1.82 (95% CI, 0.67 to 4.97)	NR
	ATLANTIS B 1999	OR[c] = 1 (95% CI, 0.08 to 11.78)	NR
	ATLANTIS A 2000	OR[c] = 11.38 (95% CI, 1.04 to 124.06)	NR
	NINDS 1995	OR[c] = 0.81 (95% CI, 0.54 to 1.21)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS III = The Third European Cooperative Acute Stroke Study; HR = hazard ratio; IST-3 = third International Stroke Trial; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SR = systematic review TESPI = The Thrombolysis in Elderly Stroke Patients in Italy.

[a]Adjusted for age, NIHSS score, and time of randomization.

[b]Further results for secondary end points and sensitivity analyses are presented in the article and are not shown here.

[c]Not reported whether effect estimate is adjusted.

[d]Positive values indicate fewer deaths with alteplase (as reported in the publication).

[e]Further results for different follow-up times and groups of patients are presented in the article and are not shown here.

Table 7: Summary of Findings for Alteplase Administered Within 3 Hours of Stroke — Symptomatic Intracranial Hemorrhage

Study citation and study design	Trial(s)	Effect estimate (CI)	P value
36-hour follow-up			
Chen et al. (2020)[18] SR Results from MA	ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP and others	OR[a,b] (pooled) = 1.00 (95% CI, 0.55 to 1.82)	NR
7-day follow-up			
Lindley et al. (2015)[21] RCT	IST-3	OR[c] = 8.80 (99% CI, 2.21 to 35.10)	NR
3-month follow-up			
Lorenzano et al. (2021)[22] RCT[d]	TESPI	RR[a,e] = 1.15 (95% CI, 0.35 to 3.85)	1.0
Follow-up time not reported			
Lan et al. (2019)[19] SR Results from 2 RCTs	NINDS	OR[a] = 1.19 (95% CI, 0.05 to 30.79)	NR
	PRISMS	OR[a] = 2.31 (95% CI, 0.78 to 6.80)	NR
Wardlaw et al. (2014)[13] SR Results from 4 RCTs	ECASS II 1998	OR[a] = 1.6 (95% CI, 0.39 to 6.61)	NR
	ATLANTIS B 1999	OR[a] = 20.09 (95% CI, 0.31 to 1,283.97)	NR
	ATLANTIS A 2000	OR[a] = 10.07 (95% CI, 0.58 to 174.52)	NR
	NINDS 1995	OR[a] = 5.44 (95% CI, 2.32 to 12.73)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study; IST-3 = third International Stroke Trial; MA = meta-analysis; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; OR = odds ratio; PRISMS = The Potential of rtPA for Ischemic Strokes With Mild Symptoms; RCT = randomized controlled trial; RR = relative risk; SITS-MOST = Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SR = systematic review; TESPI = The Thrombolysis in Elderly Stroke Patients in Italy.

[a]Not reported whether effect estimate is adjusted.

[b]SITS-MOST definition for sICH used.

[c]Adjusted for age, NIHSS score, and time of randomization.

[d]Further results for fatal sICH and sICH using different definitions are presented in the article and are not shown here.

[e]NINDS definition used for sICH used.

Table 8: Summary of Findings for Alteplase Administered Within 3 Hours of Stroke — Functional Outcomes

Study citation and study design	Trial(s)	Definition	Effect estimate (CI) or group values	P value
7-day follow-up				
Lorenzano et al. (2021)[22] RCT[a]	TESPI	Neurologic improvement (NIHSS score ≥ 4 or score 0 to 1)	Alteplase: 64.8% Control: 50.5%	0.047

Study citation and study design	Trial(s)	Definition	Effect estimate (CI) or group values	P value
3-month follow-up				
Lorenzano et al. (2021)[22] RCT[a]	TESPI	Alive and independent (mRS 0 to 2)	RR[b] = 1.25 (95% CI, 0.76 to 2.05)	0.381
Chen et al. (2020)[18] SR Results from MA	ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP and others	Favourable outcome (mRS 0 to 1)	OR[b] (pooled) = 1.62 (95% CI, 1.37 to 1.92)	NR
Lan et al. (2019)[19] SR Results from 2 RCTs	NINDS	Functional outcome (mRS 0 to 2)	OR[b] = 0.85 (95% CI, 0.20 to 3.63)	NR
	PRISMS	Functional outcome (mRS 0 to 2)	OR[b] = 0.66 (95% CI, 0.30 to 1.47)	NR
6-month follow-up				
Lindley et al. (2015)[21] RCT	IST-3	Functional outcome (OHS 0 to 2)	OR[c] = 1.50 (99% CI, 1.03 to 2.19)	NR
Follow-up time not reported				
Wardlaw et al. (2014)[13] SR[d] Results from 4 RCTs	ECASS II 1998	Alive and favourable outcome (mRS 0 to 2)	OR[b] = 1.2 (95% CI, 0.63 to 2.26)	NR
	ATLANTIS B 1999		OR[b] = 3.89 (95% CI, 1.04 to 14.52)	NR
	ATLANTIS A 2000		OR[b] = 0.39 (95% CI, 0.07 to 2.24)	NR
	NINDS 1995		OR[b] = 2.03 (95% CI, 1.46 to 2.82)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study; IST-3 = third international stroke trial; MA = meta-analysis; mRS = modified Rankin scale; NA = not applicable; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; OHS = Oxford Handicap Scale; OR = odds ratio; PRISMS = The Potential of rtPA for Ischemic Strokes With Mild Symptoms; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; TESPI = The Thrombolysis in Elderly Stroke Patients in Italy.

[a]Further results for different functional outcomes using different definitions are presented in the article and are not shown here.

[b]Not reported whether effect estimate is adjusted.

[c]Adjusted for age, NIHSS score, and time of randomization.

[d]Further results for death or dependency outcomes are presented in the article and are not shown here.

Table 9: Summary of Findings for Alteplase Administered Within 3 Hours of Stroke — Adverse Events

Study citation and study design	Trial	Variable	Total	Alteplase	Standard care	P value
3-month follow-up						
Lorenzano et al. (2021)[22] RCT[a]	TESPI	All adverse events[b]	69 (36.1%)	34 (38.6%)	35 (34.0%)	0.506
		Serious adverse events[b]	35 (18.3%)	19 (21.6%)	16 (15.5%)	0.282

RCT = randomized controlled trial; TESPI = The Thrombolysis in Elderly Stroke Patients in Italy

[a]Further results by adverse event type are presented in the article and are not shown here.

[b]Defined as at least 1 event. Definitions of adverse events were unclear.

Table 10: Summary of Findings for Alteplase Administered 3 Hours to 4.5 Hours After Stroke — Mortality

Study citation and study design	Trial(s)	Effect estimate (CI)	P value
7-day follow-up			
Alper et al. (2020)[14] Re-analysis of an RCT[a]	Re-analysis of the ECASS III trial	RR[b] = 1.06 (95% CI, 0.50 to 2.28)	0.877
		RR[c] = 1.05 (95% CI, 0.49 to 2.22)	0.902
Lindley et al. (2015)[21] RCT	IST-3	OR[d] = 1.82 (99% CI, 1.07 to 3.10)	NR
3-month follow-up			
Alper et al. (2020)[14] Re-analysis of an RCT[a]	Re-analysis of the ECASS III trial	RR[b] = 1.05 (95% CI, 0.65 to 1.69)	0.846
		RR[c] = 0.99 (95% CI, 0.61 to 1.60)	0.953
Chen et al. (2020)[18] SR Results from MA	ATLANTIS, A NINDS, ECASS II, ECASS III, WAKE-UP and others	OR[e] (pooled results) = 0.74 (95% CI, 0.49 to 1.13)	NR
Follow-up time not reported			
Lan et al. (2019)[19] SR Results from 1 RCT	PRISMS	OR[e] = 3.04 (95% CI, 0.12 to 75.16)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study; IST-3 = third international stroke trial; MA = meta-analysis; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; OR = odds ratio; PRISMS = The Potential of rtPA for Ischemic Strokes With Mild Symptoms; RCT = randomized controlled trial; RR = relative risk; SR = systematic review

[a]Further effect estimates and sensitivity analyses are presented in the article and are not shown here.

[b]Model included NIHSS score, treatment assignment, history of prior stroke, other covariates (if significant baseline imbalances).

[c]Analysis stratified results by NIHSS score and history of prior stroke.

[d]Adjusted for age, NIHSS score, and time of randomization.

[e]Not reported whether effect estimate is adjusted.

Table 11: Summary of Findings for Alteplase Administered 3 Hours to 4.5 Hours After Stroke — Symptomatic Intracranial Hemorrhage

Study citation and study design	Trial(s)	Effect estimate (CI)	P value
36-hour follow-up			
Chen et al. (2020)[18] SR Results from MA	ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP and others	OR[a] (pooled) = 2.49 (95% CI, 0.83 to 7.43)	NR

Study citation and study design	Trial(s)	Effect estimate (CI)	P value
7-day follow-up			
Alper et al. (2020)[14] Re-analysis of an RCT[b]	Re-analysis of the ECASS III trial	RR[c] (ECASS II definition) = 2.33 (95% CI, 1.08 to 5.01)	0.030
		RR[d] (ECASS II definition) = 2.17 (95% CI, 1.01 to 4.64)	0.041
		RR[c] (NINDS definition) = 2.37 (95% CI, 1.31 to 4.29)	0.004
		RR[d] (NINDS definition) = 2.32 (95% CI, 1.23 to 4.39)	0.007
Lindley et al. (2015)[21] RCT	IST-3	OR[e] = 6.30 (99% CI, 2.16 to 18.34)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study; IST-3 = third international stroke trial; MA = meta-analysis; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SR = systematic review.

[a]Not reported whether effect estimate is adjusted.

[b]Further effect estimates and sensitivity analyses are presented in the article and are not shown here.

[c]Model included NIHSS score, treatment assignment, history of prior stroke, other covariates (if significant baseline imbalances).

[d]Analysis stratified results by NIHSS score and history of prior stroke.

[e]Adjusted for age, NIHSS score, and time of randomization.

Table 12: Summary of Findings for Alteplase Administered 3 Hours to 4.5 Hours After Stroke — Functional Outcomes

Study citation and study design	Trial	Definition	Effect estimate (CI)	P value
3-month follow-up				
Alper et al. (2020)[14] Re-analysis of an RCT[a]	Re-analysis of the ECASS III trial	Symptom-free status (mRS 0)	RR[b] = 1.11 (95% CI, 0.88 to 1.39)	0.395
			RR[c] = 1.19 (95% CI, 0.94 to 1.50)	0.140
		Disability-free status (mRS 0 to 1)	RR[b] = 1.05 (95% CI, 0.95 to 1.16)	0.324
			RR[c] = 1.09 (95% CI, 0.96 to 1.24)	0.163
		Dependence-free status (mRS 0 to 2)	RR[b] = 1.01 (95% CI, 0.95 to 1.06)	0.848
			RR[c] = 1.04 (95% CI, 0.95 to 1.14)	0.397
		Dependence (Barthel Index ≥ 95)	RR[b] = 1.00 (95% CI, 0.95 to 1.06)	0.949
			RR[c] = 1.04 (95% CI, 0.94 to 1.14)	0.463
		Favourable neurologic outcome (NHISS 0 or 1)	RR[b] = 1.05 (95% CI, 0.95 to 1.16)	0.375
			RR[c] = 1.09 (95% CI, 0.95 to 1.23)	0.214
		Independence (Glasgow Outcome Scale 1)	RR[b] = 1.03 (95% CI, 0.93 to 1.15)	0.568
			RR[c] = 1.07 (95% CI, 0.94 to 1.21)	0.310
		Functional outcome (Global outcome)	RR[b] = 1.14 (95% CI, 0.87 to 1.50)	0.335

Study citation and study design	Trial	Definition	Effect estimate (CI)	P value
Chen et al. (2020)[18] SR Results from MA	ATLANTIS A, NINDS, ECASS II, ECASS III, WAKE-UP and others	Favourable outcome (mRS 0 to 1)	OR[d] (pooled) = 1.18 (95% CI, 1.05 to 1.32)	NR
6-month follow-up				
Lindley et al. (2015)[21] RCT	IST-3	Functional outcome (OHS 0 to 2)	OR[e] = 1.06 (99% CI, 0.78 to 1.44)	NR

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study; IST-3 = third international stroke trial; MA = meta-analysis; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; OHS = Oxford Handicap Scale; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SR = systematic review.

[a]Further effect estimates, and sensitivity analyses are presented in the article and are not shown here.

[b]Model included NIHSS score, treatment assignment, history of prior stroke, other covariates (if significant baseline imbalances).

[c]Analysis stratified results by NIHSS score and history of prior stroke.

[d]Not reported whether effect estimate is adjusted.

[e]Adjusted for age, NIHSS score, and time of randomization.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix was not copy-edited.

Table 13: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Major stroke trial	Primary study citation(s)[a]	Chen 2020[18]	Lan 2019[19]	Wardlaw 2014[13]
ATLANTIS A	Clark WM, et al. Stroke 2000;31(4):811 to 6.	Yes	—	Yes
ATLANTIS B	Albers GW, et al. Stroke. 2002;33(2):493 to 495.	—	—	Yes
	Clark WM, et al. JAMA 1999;282(21):2019 to 26.			
ECASS II	Hacke W, et al. Lancet. 1998;352(9136):1245 to 1251.	Yes	—	Yes
ECASS III	Hacke W, et al. N Engl J Med. 2008;359(13):1317 to 1329.	Yes	—	Yes
NINDS	Khatri P, et al. Stroke. 2010;41(11):2581 to 2586.	Yes	Yes	Yes
	The National Institute of Neurological Disorders and Stroke rt-PA stroke study group. N Eng J Med. 1995;333(24):1581 to 7.			
PRISMS	Khatri P, et al. JAMA. 2018;320(2):156 to 166.	—	Yes	—
WAKE-UP	Barow E, et al. JAMA Neurol. 2019;76(6):641 to 649.	Yes	—	—
NA	Antoncić I, et al. Coll Antropol. 2011;35(2):483 to 486.	Yes	—	—
NA	Zhang B, et al. Eur Neurol. 2011;65(3):170 to 174.	Yes	—	—

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS = European Cooperative Acute Stroke Study; IST-3 = third international stroke trial; NA = not applicable; NINDS = National Institute of Neurological Disorders and Stroke; PRISMS = The Potential of rtPA for Ischemic Strokes With Mild Symptoms
a = For Chen 2020 and Lan 2019, the primary study citations are provided. For Wardlaw 2014, the citation for the major publication of the stroke trial is given since several publications were used to obtain data for each stroke trial.

Appendix 6: References of Potential Interest

Note that this appendix was not copy-edited.

Meta-Analyses Without Systematic Review

Lorenzano S, Vestri A, Lancia U, et al. Thrombolysis In Elderly Stroke Patients in Italy (TESPI) trial and updated meta-analysis of randomized controlled trials. *Int J Stroke.* 2021;16(1):43-54. PubMed

Lees KR, Emberson J, Blackwell L, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. *Stroke.* 2016;47(9):2373-2379. PubMed

Whiteley WN, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. *Lancet Neurol.* 2016;15(9):925-933. PubMed

Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384(9958):1929-1935. PubMed

Non-English Systematic Review

Smedslund G, Myrhaug HT, Hov L, Kirkehei I. NIPH systematic reviews: executive summaries. Oslo (NO): Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH);2016.

Systematic Review Protocols

Ni LY, Tang JY. Clinical safety and outcome of recombinant tissue plasminogen activator in patients with stroke attributable to small artery occlusion: a protocol for systematic review and meta-analysis. *Medicine.* 2021;100(25):e26453. PubMed

Huang B, Qian F, Fan X, et al. Efficacy and safety of intravenous thrombolysis with alteplase for treating acute ischemic stroke at different time windows: a protocol for systematic review and meta-analysis. *Medicine.* 2020;99(52):e23620. PubMed

Systematic Reviews With Included Studies Already Summarized in the Current Report

Donaldson L, Fitzgerald E, Flower O, Delaney A. Review article: why is there still a debate regarding the safety and efficacy of intravenous thrombolysis in the management of presumed acute ischaemic stroke? A systematic review and meta-analysis. *Emerg Med Australas.* 2016;28(5):496-510. PubMed

Kumar G, Uhrig D, Fowler S, DeLaney MC, Alexandrov AV. Intravenous recombinant tissue plasminogen activator does not impact mortality in acute ischemic stroke at any time point up to 6 months: a systematic review and meta-analysis of randomized controlled clinical trials. *CNS Drugs.* 2015;29(8):659-66. PubMed