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# Optimized Timing of Thrombolytic Therapy for the Treatment of Stroke: A Rapid Review

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## Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy makers.

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# List of Abbreviations

| | |
|---|---|
| **CI** | Confidence interval(s) |
| **HQO** | Health Quality Ontario |
| **MRS** | Modified Rankin score |
| **OR** | Odds ratio |
| **OHTAC** | Ontario Health Technology Advisory Committee |
| **RCT** | Randomized controlled trial |
| **RT-PA** | Recombinant tissue plasminogen activator |
| **SICH** | Symptomatic intracranial hemorrhage |

# Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Funding (QBF) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Funding initiative, visit www.hqontario.ca.

## Objective of Analysis

The objective of this analysis is to determine the optimal timing for the administration of thrombolytic therapy for stroke to maximize patient independence and minimize the risk of symptomatic intracranial hemorrhage (SICH).

## Clinical Need and Intervention

### Acute Ischemic Stroke

Ischemic strokes account for 80% of strokes, and result from the blockage of oxygen and blood flow to the brain. (1) Pending confirmation of the absence of intracranial hemorrhage with diagnostic imaging, thrombolysis via mechanical or pharmaceutical means may be undertaken to obliterate the obstructing clot. This intervention has demonstrated marked improvement in the prognosis for stroke patients. (2) In addition to the mitigation of damage to brain tissue, functional outcomes have been cited as the most clinically relevant for stroke patients, with a focus on maximizing independence among stroke survivors. (3)

## Technique

For decades, thrombolytic pharmaceuticals that dissolve clots have been a mainstay of cardiology in the treatment of myocardial infarction. (4) There are several such pharmaceutical agents, including streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA). Currently, intravenous rt-PA is approved by Health Canada for use in adults with acute ischemic stroke within three hours of symptom onset. (2) Clinical trials and subsequent meta-analyses highlight a fine balance between the positive functional outcomes with rt-PA and the risk of serious adverse effects, especially symptomatic intracranial hemorrhage (SICH), which is associated with the decline of a patient's mental state. (3) This risk-benefit relation partly depends on the timing of treatment with rt-PA relative to stroke onset, and the currently approved administration window of 0 to 3 hours after onset is informed primarily by a pivotal clinical trial from 1995. (5) More recent trials have suggested that rt-PA treatment beyond 3 hours of onset may also be beneficial. However, randomized controlled trials (RCTs) have generally been unable to yield statistically significant or consistent findings.

# Rapid Review

## Research Question

What is the optimal time window after ischemic stroke onset to administer thrombolytics to maximize patient independence and minimize risk of symptomatic intracerebral hemorrhage (SICH)?

## Research Methods

### Literature Search

A literature search was performed on November 8, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, until November 8, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

### Inclusion Criteria

- English language full-reports
- published between January 1, 2008, and November 8, 2012
- health technology assessments, systematic reviews, and meta-analyses
- acute ischemic stroke patients receiving pharmaceutical thrombolysis in hospital

### Exclusion Criteria

- randomized controlled trials, observational studies, case reports, editorials, letters to the editor
- mechanical and/or combination thrombolytic interventions
- patient populations other than ischemic stroke (e.g., myocardial infarction)

### Outcomes of Interest

- independence (a functional outcome characterized by a lack or low level of dependency)
- symptomatic intracranial hemorrhage (SICH)

### Expert Panel

In August 2012, an Expert Advisory Panel on Episodes of Care for Stroke was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representation from the field of stroke care.

The role of the Expert Advisory Panel on Episodes of Care for Stroke was to contextualize the evidence produced by HQO, and to provide advice on the components of a high-quality episode of care for stroke patients presenting to an acute-care hospital. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of expert advisory panel members.

# Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool is used to assess the methodological quality of systematic reviews. (6) The highest-rated review was assessed to address the research question, and primary studies from systematic reviews were acquired and referenced as necessary.

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (7) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (7) For more detailed information, please refer to the latest series of GRADE articles. (7)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

| | |
|---|---|
| **High** | Very confident that the true effect lies close to the estimate of the effect |
| **Moderate** | Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| **Low** | Confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect |
| **Very Low** | Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect |

# Results of Literature Search

The database search yielded 517 citations published between January 1, 2008, and November 8, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were acquired for further assessment.

Two meta-analyses addressing the question of optimal timing for the administration of recombinant tissue plasminogen activator (rt-PA) met the inclusion criteria. (8;9) No articles examining the timing of administration of other thrombolytic medications were identified via the search.

The AMSTAR score of the Maiser et al (8) meta-analysis was 5 out of a possible 11, and the Wardlaw et al (9) meta-analysis, which was an update to a Cochrane Systematic Review (3), scored an 8 (see Appendix 3). Given the higher methodological quality as judged by AMSTAR, and that all of the primary studies (4 RCTs) included in the Maiser meta-analysis were included in the Wardlaw meta-analysis (in addition to several other RCTs), this article was used to answer the research question. As the scope of the 2012 Wardlaw meta-analysis was more focused, the full Cochrane review that this article updates was referred to on a *pro re nata* basis only, with data extraction and evidence quality assessment based predominantly on the references that comprise the 2012 meta-analysis.

Eight RCTs were analyzed by Wardlaw et al (9) to evaluate the optimal timing for the administration of rt-PA, with consideration to the outcomes of independence and SICH. Of the 8 studies, 1 contributed data only for patients administered rt-PA within 0 to 3 hours of stroke onset (10) and 2 contributed data only for rt-PA treatment within the 3 to 6 hour window. (11;12) The remaining 5 RCTS contributed data on both time windows (Table 1). (13-17)

**Table 1: RCT's Contributing Data to the Comparison of 0 to 3 Hour Versus 3 to 6 Hour Time Window of rt-PA Therapy for Acute Ischemic Stroke**

| Full Trial Name, Year | Trial Acronym | Sample Size | Timing Data Contributed | |
|---|---|---|---|---|
| | | | 0-3h after onset | 3-6h after onset |
| The National Institute of Neurological Disorders and Stroke, 1995 (10) | NINDS | 624 | ✓ | |
| The European Cooperative Acute Stroke Study, 1995 (15) | ECASS | 620 | ✓ | ✓ |
| The European Cooperative Acute Stroke Study II, 1998 (16) | ECASS II | 800 | ✓ | ✓ |
| The Thrombolytic Therapy in Acute Ischemic Stroke Study Part B, 1999 (13) | ATLANTIS B | 613 | ✓ | ✓ |
| The Thrombolytic Therapy in Acute Ischemic Stroke Study Part A, 2000 (14) | ATLANTIS A | 142 | ✓ | ✓ |
| The European Cooperative Acute Stroke Study 3, 2008 (12) | ECASS 3 | 821 | | ✓ |
| The Echoplanar Imaging Thrombolytic Evaluation Trial, 2008 (11) | EPITHET | 101 | | ✓ |
| The Third International Stroke Trial, 2012 (17) | IST-3 | 3,035 | ✓ | ✓ |

Abbreviations: CI, confidence intervals; H, hours; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator.
*Source: Wardlaw et al, 2012 (9).*

The results of the comparisons by treatment time subgroups are presented in Table 2. The likelihood of patients being alive and independent 90 days post-treatment was statistically significantly higher in the

group treated with rt-PA within 3 hours of stroke onset, compared with patients treated within 3 to 6 hours. No statistically significant difference in the risk of SICH between groups was found.

**Table 2: Comparison of Independence and Symptomatic Intracranial Hemorrhage for Stroke Patients Administered Recombinant Tissue Plasminogen Activator (rt-PA) or Placebo within 0 to 3 Hours versus 3 to 6 Hours of Acute Ischemic Stroke**

| Outcome | Definition | Follow-up Time | Odds Ratio 0–3 h (95% CI) | Odds Ratio 3–6 h (95% CI) | $X^2$ (df) | *P* value |
|---|---|---|---|---|---|---|
| Symptomatic Intracranial Hemorrhage | Worsening of neurological status and the concurrent appearance of new hemorrhage on brain imaging sufficient to cause neurological deterioration | within 7 days | 4.55 (2.92–7.09) | 3.73 (2.86–4.86) | 0.57 (2) | 0.45 |
| Alive and Independent | Modified Rankin Score of 0–2[a] | at 90 days | 1.53 (1.26–1.86) | 1.07 (0.96–1.20) | 9.49 (2) | 0.002 |

Abbreviations: CI, confidence intervals; DF, degrees of freedom; H, hours; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator.
[a]Barthel Index (BI) and Oxford Handicap Scores (OHS) for independence measures from trials were converted to Modified Rankin Score (mRS) equivalencies by the authors (i.e., BI ≥ 65 = mRS 0–2; OHS 0–2 = mRs 0–2).
*Source: Wardlaw et al, 2012 (9).*

The absolute effect for the increase in SICH was estimated to be 68 (95% CI: 49 to 87) and 58 (95% CI: 46 to 70) per 1,000 patients treated for the 0- to 3-hour and the 3- to 6-hour treatment groups, respectively. Despite this considerable increase in SICH within 7 days of treatment, an increase in functional benefit occurred. For patients treated with rt-PA within 0 to 3 and 3 to 6 hours, 90 (95% CI: 46 to 135) and 18 (95% CI: -10 to 45) per 1,000 patients, respectively, were alive and independent at 90 days.

Among patients who both did and did not experience a SICH within 7 days of treatment, those treated within 3 hours of onset had a significant improvement in functional status at 90 days. However, for those treated between 3 and 6 hours after onset, a significant risk with only a marginal functional benefit was seen, suggesting that caution is warranted in treatment with rt-PA past 3 hours from onset. The risks and benefits ought to be considered by providers, patients, and families. The authors conclude that earlier treatment (i.e., within 3 hours) is better. However, the latest time window at which benefit is no longer seen cannot be determined from this meta-analysis. The Canadian Stroke Network has extended the recommended time window for rt-PA treatment to 4.5 hours after onset in light of promising findings indicating that benefit extends beyond 3 hours. (2) The Wardlaw meta-analysis only examined the aforementioned treatment times, and acknowledges that there is a need for further refinement of the optimal time window. (9)

This addition to a periodically updated Cochrane review (3) includes data from one of the largest and most recent additions to the literature on rt-PA therapy in stroke. The IST-3 was unique relative to the other RCTs in terms of trial design as it was designed with an open control and pragmatically, to include a wide range of stroke patients (in terms of ages, timing of treatment, and stroke severity). The inclusivity and lack of double-blind and placebo-control design has inherent trade-offs in terms of the rigour of RCTs that make them less susceptible to bias. Unlike preceding trials, no upper age limit was set for eligibility and, as a result, 53% of participants in this trial were aged 80 years or older. Similar benefit was seen for these patients, especially when treated within 3 hours. (9) Generally, baseline characteristics, concomitant therapies, durations of follow-up, and measurement of outcomes were comparable across the body of

evidence. A great deal of work was undertaken by Wardlaw et al (3) for the Cochrane review to acquire, translate, clarify, and synthesize data on this topic.

Detail on the assessment of the quality of this evidence is found in GRADE tables in Appendix 2.

# Conclusions

- Two meta-analyses were identified that examined the optimal timing of thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA). After assessment of methodological quality, and overlap between the articles, one meta-analysis—by Wardlaw et al—was selected.

- Treatment with rt-PA within 0 to 3 hours after stroke onset was significantly better than treatment within 3 to 6 hours (which was not statistically significant), and led to an increased number of patients who were alive and independent at 90 days. (GRADE quality of evidence: moderate)

- There was a significant increase in risk of symptomatic intracranial hemorrhage within 7 days of treatment for patients who received rt-PA both 0 to 3 hours and 3 to 6 hours after stroke onset, with no significant difference between time windows. The significant functional benefit at 90 days observed in those treated within 0 to 3 hours occurred despite this initial increase in risk of hemorrhage. (GRADE quality of evidence: moderate)

- Given the lack of evidence to support improved outcomes, coupled with the risk of intracerebral hemorrhage for patients receiving rt-PA more than 3 hours after stroke onset, the use of this intervention cannot be recommended for these patients.

# Acknowledgements


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**Expert Panel for Health Quality Ontario: 'Episode of Care' for Stroke**

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| Ms. Christina O'Callaghan | Executive Director | Ontario Stroke Network |
| Dr. Gustavo Saposnik | Director, Stroke Outcomes Research Centre,<br>Associate Professor of Medicine,<br>Division of Neurology, St. Michael's Hospital | Institute for Clinical Evaluative Sciences,<br>University of Toronto |
| Dr. Richard Swartz | Director,<br>University of Toronto Stroke Program<br>Medical Director, NE-GTA Regional Stroke Program,<br>Associate Professor,<br>Division of Neurology,<br>Department of Medicine | Sunnybrook Health Sciences Centre,<br>University of Toronto |
| Dr. Robert Teasell | Professor of Physical Medicine and Rehabilitation,<br>Schulich School of Medicine | Western University<br>Lawson Research Institute<br>St. Joseph's Health Care London |
| Dr. Paul E. Cooper | Senior Medical Director – Medicine,<br>Chief, Department of Clinical Neurological Sciences | London Health Sciences Centre |
| Dr. Paul Ellis | Emergency Physician | University Health Network |
| Dr. Andrew Samis | Physician Stroke Champion and Staff Intensivist,<br>Division of Critical Care | Quinte Health Care,<br>Belleville Ontario |
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| Name | Role | Organization |
|---|---|---|
| Dr. Murray Krahn | Director, THETA,<br>F. Norman Hughes Chair and Professor,<br>Department of Medicine and Faculty of Pharmacy | University of Toronto |
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| Lori Marshall | Executive Vice President,<br>Strategy, Performance and Aboriginal Health | Thunder Bay Regional Health Sciences Centre |
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| Derek Leong | Clinical Pharmacist,<br>General Internal Medicine | University Health Network – Toronto General Hospital |
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| Thomas Smith | Acting Program Manager, | Ministry of Health and Long-Term Care |

| Name | Role | Organization |
|---|---|---|
| | Provincial Programs Branch | |

# Appendices

## Appendix 1: Literature Search Strategies

**Search date:** November 8, 2012
**Databases searched:** OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD
**Limits:** 2008-current; English
**Filters**: health technology assessments, systematic reviews, meta-analyses

Database: Ovid MEDLINE(R) <1946 to October Week 4 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 6, 2012>, Embase <1980 to 2012 Week 44>
Search Strategy:

1 exp Stroke/ or exp brain ischemia/
2 exp intracranial hemorrhages/ use mesz
3 exp brain hemorrhage/ use emez
4 exp stroke patient/ use emez
5 (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain adj2 isch?emia) or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab.
6 or/1-5
7 exp Thrombolytic Therapy/ use mesz
8 exp Tissue Plasminogen Activator/ use mesz
9 exp fibrinolytic agent/ use emez
10 exp plasminogen activator/ use emez
11 (thromboly* or fibrinoly*).ti,ab.
12 (plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).ti,ab.
13 (anistreplase or activase or alteplase or duteplase or lanoteplase or lumbrokinase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk).ti,ab.
14 or/7-13
15 6 and 14
16 limit 15 to english language
17 limit 16 to yr="2008 -Current"
18 Meta Analysis.pt.
19 Meta Analysis/ use emez
20 Systematic Review/ use emez
21 exp Technology Assessment, Biomedical/ use mesz
22 Biomedical Technology Assessment/ use emez
23 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.
24 ((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.
25 or/18-24
26 17 and 25
27 remove duplicates from 26

**Cochrane Library**

| ID | Search |
|---|---|
| #1 | MeSH descriptor: [Stroke] explode all trees |
| #2 | MeSH descriptor: [Brain Ischemia] explode all trees |

| | |
|---|---|
| #3 | MeSH descriptor: [Intracranial Hemorrhages] explode all trees |
| #4 | (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain near/2 isch?emia) or (cerebral near/2 isch?emia) or (intracranial near/2 hemorrhag*) or (brain near/2 hemorrhag*)):ti or (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain near/2 isch?emia) or (cerebral near/2 isch?emia) or (intracranial near/2 hemorrhag*) or (brain near/2 hemorrhag*)):ab |
| #5 | #1 or #2 or #3 or #4 |
| #6 | MeSH descriptor: [Thrombolytic Therapy] explode all trees |
| #7 | MeSH descriptor: [Tissue Plasminogen Activator] explode all trees |
| #8 | thromboly* or fibrinoly*:ti,ab,kw (Word variations have been searched) |
| #9 | plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA:ti,ab,kw (Word variations have been searched) |
| #10 | anistreplase or activase or alteplase or duteplase or lanoteplase or lumbrokinase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk:ti,ab,kw (Word variations have been searched) |
| #11 | #6 or #7 or #8 or #9 or #10 |
| #12 | #5 and #11 from 2008 to 2012 |
| #13 | #12 in Trials |
| #14 | #12 not #13 |

**CRD**

| Line | Search |
|---|---|
| 1 | MeSH DESCRIPTOR stroke EXPLODE ALL TREES |
| 2 | MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES |
| 3 | MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES |
| 4 | (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain adj2 isch?emia) or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)) |
| 5 | #1 OR #2 OR #3 OR #4 |
| 6 | MeSH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES |
| 7 | MeSH DESCRIPTOR Tissue Plasminogen Activator EXPLODE ALL TREES |
| 8 | (thromboly* or fibrinoly*) |
| 9 | (plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA) |
| 10 | (anistreplase or activase or alteplase or duteplase or lanoteplase or lumbrokinase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk) |
| 11 | #6 OR #7 OR #8 OR #9 OR #10 |
| 12 | #5 AND #11 |
| 13 | (#12) FROM 2008 TO 2012 |

# Appendix 2: AMSTAR and GRADE Tables

### Table A1: AMSTAR Scores of Systematic Reviews

| Author, Year | AMSTAR score[a] | 1) Provided Study Design | 2) Duplicate Study Selection | 3) Broad Literature Search | 4) Considered Status of Publication | 5) Listed Studies | 6) Provided Characteristics of Studies | 7) Scientific Quality Assessed | 8) Considered Quality in Report | 9) Methods to Combine Appropriate | 10) Assessed Publication Bias | 11) Stated Conflict of Interest |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Maiser, 2011 (8) | 5 | ✓ | | ✓ | | ✓ | ✓ | | | ✓ | | |
| Wardlaw, 2012 (9) | 8 | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | ✓ |

[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al (6).

### Table A2: GRADE Evidence Profile for Comparison of 0- to 3-Hour and 3- to 6-Hour Timing of Recombinant Tissue Plasminogen Activator (rt-PA) for Acute Ischemic Stroke

| No. of Studies (Design) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Upgrade Considerations | Quality |
|---|---|---|---|---|---|---|---|
| **Independence** | | | | | | | |
| 8 (RCTs) | Serious limitations (-1)[ab] | No serious limitations | No serious limitations[c] | No serious limitations | Undetected[d] | None | ⊕⊕⊕ Moderate |
| **Symptomatic Intracranial Hemorrhage** | | | | | | | |
| 8 (RCTs) | Serious limitations (-1)[ae] | No serious limitations | No serious limitations[c] | No serious limitations[f] | Undetected[d] | None | ⊕⊕⊕ Moderate |

Abbreviations: No., number; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator; SICH, symptomatic intracranial hemorrhage.

[a]One trial (IST-3) was a pragmatic trial comprised of a double-blind, placebo-controlled pilot phase followed by a main phase of open treatment. The IST-3 trial lacked blinding of providers or patients, employed masked outcome assessment, used standard care defined by each study site in lieu of placebo as a comparator, and employed a design prone to bias. Given that about half of the data (i.e., 3035 of 7012 patients) in the meta-analysis is from this trial, potential bias is a concern.

[b]One trial (EPITHET 2008) analyzed independence according to per protocol analysis instead of intention to treat. However, loss to follow-up was <15%.

[c]One trial (IST-3) did not provide an upper age limit on eligibility criteria and 53% of the sample was > 80 years old. All other trials explicitly excluded individuals in that age group due to lack of approval for use of rt-PA in older persons with acute stroke. Results on all outcomes were similar for patients both ≤ 80 and > 80 years old, suggesting indirectness is not of great concern. Health Canada and approval of rt-PA does not include stroke patients > 80 years old.

[d]3 trials (ECASS I, II, and 3) received financial support and 2 (ATLANTIS A and B) received both funding and instrumental support (e.g., data management) from industry sponsors (i.e., Gentech, Boehringer Ingelheim). These trials represent both positive and negative statistically significant and insignificant findings, and large sample sizes.

[e]Two trials (ATLANTIS B 2002, EPITHET 2008) performed per protocol analysis as opposed to intention-to-treat for safety outcomes, including SICH. However, loss to follow-up was less than 15% in both cases.

[f]The 95% confidence interval around the odds ratio for the 0 to 3h treatment group is wide (2.92–7.09), as is the case for the 3 to 6h treatment group to a lesser extent (2.86–4.86). The 95% confidence interval around the absolute effect treated is more narrow (0-3h 95% CI: 49–87 per 1,000 patients; 3-6h 95% CI: 46–87 per 1,000 patients) and this range would not change the recommended course of action. The sample size is large, the CI excludes 1.0, and the optimal information size (OIS) criterion is met, thus precision is likely adequate.

**Table A3: Risk of Bias Among Randomized Controlled Trials for the Comparison of 0- to 3-Hour and 3- to 6-Hour Timing of Recombinant Tissue Plasminogen Activator (rt-PA) for Acute Ischemic Stroke**

| Author, Year | Allocation Concealment | Blinding | Complete Accounting of Patients and Outcome Events | Selective Reporting Bias | Other Limitations |
|---|---|---|---|---|---|
| NINDS, 1995 (10) | No limitations | No limitations | No limitations | No limitations | No limitations |
| ECASS, 1995 (15) | No limitations | No limitations | No limitations | No limitations | No limitations |
| ECASS II, 1998 (16) | No limitations | No limitations | Limitations[a] | No limitations | No limitations |
| ATLANTIS B, 1999 (13) | No limitations | No limitations | No limitations | No limitations | No limitations |
| ATLANTIS A, 2000 (14) | No limitations | No limitations | No limitations | No limitations | No limitations[b] |
| ECASS 3, 2008 (12) | No limitations | No limitations | No limitations | No limitations | No limitations |
| EPITHET, 2008 (11) | No limitations | No limitations | Limitations[c] | No limitations | No limitations |
| IST-3, 2012 (17) | Limitations[d] | Limitations[e] | No limitations | No limitations | No limitations |

Abbreviations: ATLANTIS, The Thrombolytic Therapy in Acute Ischemic Stroke Study; ECASS, The European Cooperative Acute Stroke Study; EPITHET, The Echoplanar Imaging Thrombolytic Evaluation Trial; IST-3, The Third International Stroke Trial; NINDS, The National Institute of Neurological Disorders and Stroke; RCT, randomized controlled trial.

[a]Some outcomes were analyzed according to intention-to-treat protocol, and others were per protocol.

[b]ATLANTIS A aimed to enroll 300 patients but was stopped early for safety concerns in the group receiving rt-PA between 5 and 6 hours. The trial protocol was redesigned to allow treatment only up to 5 hours and conducted as a new trial, ATLANTIS B. The authors state that these trials are considered and presented as separate trials for analysis.

[c]All results were based on per protocol analysis. Loss to follow-up did not exceed 15% per group or overall.

[d]Randomization was generated by central telephone system, however, both patients and providers were aware of group allocation due to open-treatment design.

[e]Blinding of care providers or patients was not part of the study due to the open-treatment design. Outcome and follow-up assessments at 6 months were masked.

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