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Effectiveness and Safety of Thrombolytics for the Treatment of Ischemic Stroke: A Rapid Review

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Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

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.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

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.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

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List of Abbreviations

CI	confidence interval(s)
HQO	Health Quality Ontario
OR	odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	randomized controlled trial
rt-PA	Recombinant tissue plasminogen activator

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 rapid review is to determine the effectiveness and safety of thrombolytics administered as part of the treatment for ischemic stroke.

Clinical Need and Technology

Ischemic stroke is the result of an interruption of blood flow to the brain. Among patients who have a stroke, approximately 80% are ischemic. (1) The primary acute treatment objective for a patient presenting with an ischemic stroke is the reperfusion to the brain tissue at the site of the blood supply blockage. (2)

Intravenous administration of the recombinant tissue plasminogen activator (rt-PA) was the first Health Canada approved pharmaceutical thrombolytic treatment for ischemic stroke. (2) Originally, rt-PA was approved for administration within 3 hours of onset of stroke. However, the Canadian Stroke Network has recently referenced research that suggests this may be extended to up to 4.5 hours. (2) The Canadian Stroke Network also recommends that best practice includes the administration of rt-PA within 60 minutes of presentation to the emergency department. (2) Overall, only 8% of patients with ischemic stroke receive rt-PA. (2) However, among those who do receive it, 49% receive rt-PA within the first 2 hours of onset of symptoms. (2)

Other reperfusion strategies include intra-arterial administration of thrombolytics, mechanical thrombolysis through ultrasound or embolectomy, and combination therapies that involve the combination of mechanical and intravenous/intra-arterial thrombolytics. One systematic review that compared the different reperfusion strategies concluded that no single treatment route had greater efficiency or safety compared to the others. (3)

Rapid Review

Research Question

What is the effectiveness and safety of thrombolytics administered as part of the treatment for ischemic stroke?

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
- meta-analyses, systematic reviews, and health technology assessments
- inhospital setting
- intravenous thrombolytics therapies for ischemic stroke

Exclusion Criteria

- studies where outcomes of interest cannot be abstracted
- intra-arterial or other nonintravenous routes of administration
- nondrug thrombolysis techniques (e.g., sonothrombolytics) or combination therapies (e.g., ultrasound enhanced thrombolysis)

Outcomes of Interest

- mortality
- dependency (as a measure of degree of neurological impairment and functional ability)

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 community.

The role of the Expert Advisory Panel on Episodes of Care for Stroke was to contextualize the evidence produced by Health Quality Ontario and provide advice of a high quality episode of care for heart failure

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 (AMASTAR) tool was used to assess the quality and aid in the final selection of the systematic reviews, meta-analyses, and health technology assessments. (4) Details of the primary studies were abstracted from the review for quality assessment of the 2 outcomes of interest using GRADE as described below. The original research studies were referenced on an 'as needed' basis to supplement the information in the systematic reviews, in order to appropriately apply GRADE.

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (5) 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. (5) For more detailed information, please refer to the latest series of GRADE articles. (5)

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 obtained for further assessment.

Three reviews met the inclusion criteria. The overall quality of these reviews was fair and a detailed description of the AMASTAR ratings assigned is available in Appendix 3, Table A2. The systematic review by Wardlaw et al (6) was awarded the highest possible AMSTAR score and incorporates all of the RCTs that were included in the other reviews. Therefore, for the purposes of this rapid review, Wardlaw et al is reviewed.

Description of RCTs included

A total of 21 RCTs from the Wardlaw et al systematic review (6) are referenced in this rapid review. Among these studies there are some notable differences with respect to the inclusion criteria, length of follow-up, sample size, and, most notably, the thrombolytic agent (Appendix 2, Table A1).

Mortality

Wardlaw et al determined that the rate of all cause mortality is statistically significantly higher among patients who received any thrombolytic agent compared to control groups within 7 to 10 days of administration (random effects model: OR 1.68, 95% CI 1.22 to 2.30, p =0.001). (6)

When a subgroup analysis by type of intravenous thrombolytic therapy was conducted, some of the thrombolytic agents demonstrated a stronger relationship with mortality than others (Table 1). As a sensitivity analysis, a recalculation of the effect estimate without the streptokinase plus oral aspirin group was conducted. While the odds of death decreased, it remained statistically significantly greater among patients who received thrombolytics alone compared to the control group (Appendix 4, Figure 2).

The rt-PA group had the largest sample size in the meta-analysis by Wardlaw et al. (6) This subgroup analysis demonstrated no statistically significant association with mortality during the first 7 to 10 days among patients receiving the thrombolytic compared to the control group (Table 1).

Table 1: Subgroup Analyses of Wardlaw et al Comparison of Any Thrombolytic Agent Versus Control on All Cause Mortality[a]

Study Groups			N Included Studies	Sample Size (Intervention/Control)	OR (95% CI)
Urokinase	vs.	Control	1	317/148	1.35 (0.62 to 2.94)
Streptokinase	vs.	Control	3	487/476	1.90 (1.37 to 2.63)
rt-PA	vs.	Control	7	1292/1208	1.23 (0.88 to 1.71)
Streptokinase plus oral aspirin	vs.	Oral aspirin	1	156/153	3.86 (2.26 to 6.59)
Demoteplase	vs.	Control	1	123/63	4.73 (0.85 to 26.26)

[a] adapted from Wardlaw et al (6)

The quality of the body of evidence on mortality was assessed as moderate, indicating the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (Table A3).

Dependency

Wardlaw et al determined a statistically significant reduction in dependency, as determined by the modified Rankin scale among patients who received any thrombolytic agent compared to control groups within study follow-up periods (OR 0.67, 95% CI 0.61 to 0.75, p <0.0001; I^2 29.4%, p =0.20). (6)

When the subgroup analyses were examined, there was a greater association with dependency for some of the thrombolytics than others (Table 2). The rt-PA group was the largest, by sample size, and demonstrated a statistically significant reduction on dependency (Table 2).

Table 2: Subgroup Analyses of Wardlaw et al Comparison of Any Thrombolytic Agent Versus Control on Dependency[a]

Study Groups			N Included Studies	Sample Size (Intervention/Control)	OR (95% CI)
Intravenous urokinase	vs.	control	1	317/148	0.80 (0.53 to 1.22)
Intravenous streptokinase	vs.	control	4	497/486	0.64 (0.49 to 0.85)
Intravenous rt-PA	vs.	control	9	1967/1884	0.71 (0.62 to 0.81)
Intravenous streptokinase plus oral aspirin	vs.	Oral aspirin	1	156/153	0.36 (0.22 to 0.58)
Intra-arterial pro-urokinase plus intravenous heparin	vs.	Intravenous heparin	2	147/73	0.71 (0.41 to 1.28)
Intra-arterial urokinase	vs.	control	2	65/65	0.53 (0.26 to 1.06)
Intravenous desmoteplase	vs.	control	3	227/98	0.66 (0.41 to 1.06)

[a] adapted from Wardlaw et al, based on the modified Rankin scale 3-5 (6)

The focus of this rapid review is on thrombolytics administered intravenously. Given this analysis by Wardlaw et al included two intra-arterial thrombolytics, the effect estimate was recalculated using only the intravenous thrombolytics (Figure 1). The resulting effect estimate (OR 0.72, 95% CI 0.65 to 0.81) was on par with the effect estimate presented by Wardlaw et al and demonstrated a statistically significant reduction in dependency among patients who received an intravenous thrombolytic compared with control groups (Figure 1). When the streptokinase plus aspirin group was removed from the analysis to evaluate the use of thrombolytics alone, there again remained a statistically significant reduction in dependency among patients who received thrombolytics compared to the control groups (Appendix 4, Figure 3).

The quality of the body of evidence on dependency was assessed as *moderate*, indicating the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (Table A3).

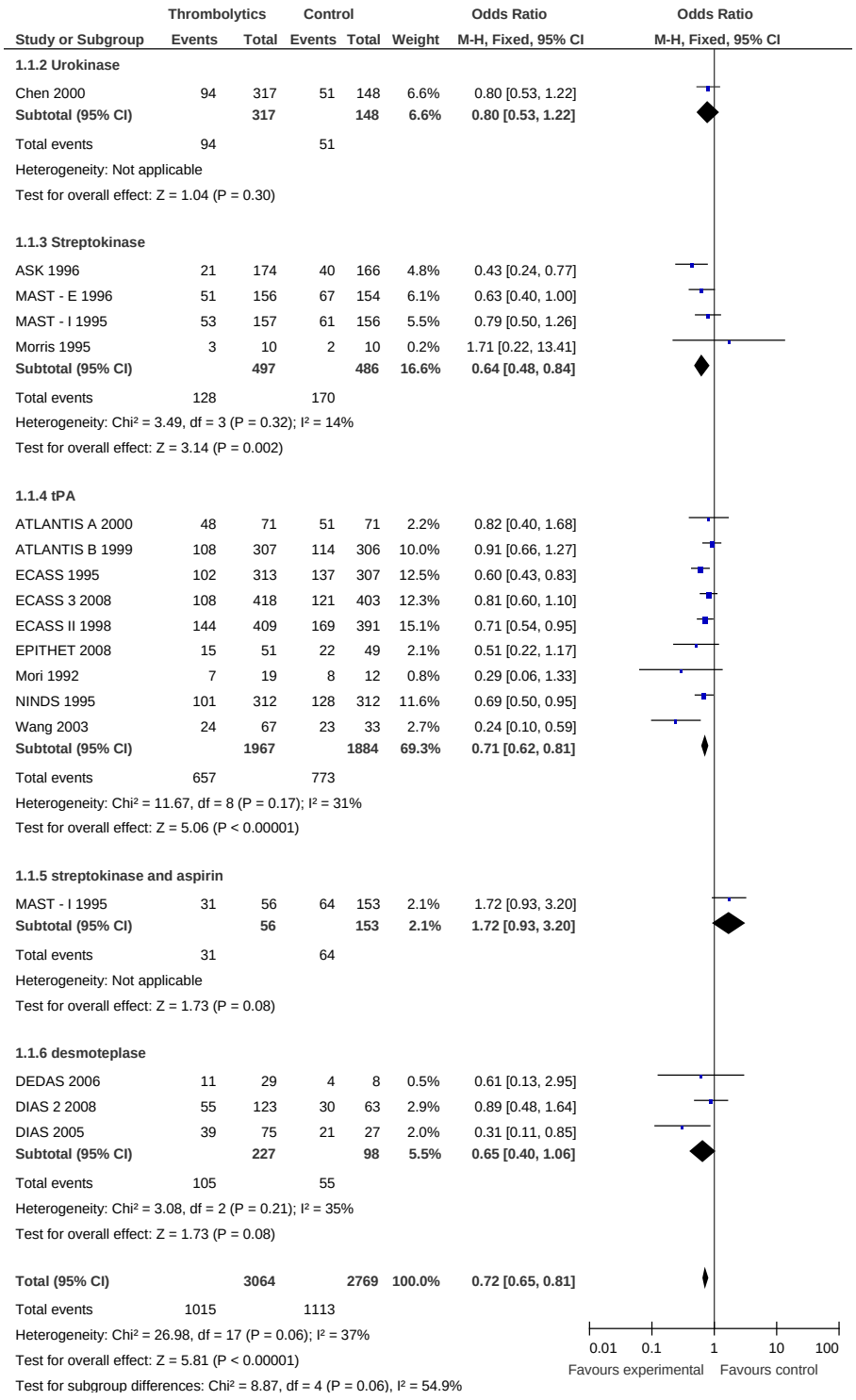

Figure 1: Forest Plot of Impact of Intravenous Thrombolytics on Dependency

Additional Outcomes of Interest

All cause mortality until end of follow-up

Wardlaw et al conducted an analysis which examined mortality until the end of follow-up, regardless of length of study. (6) As a result, Wardlaw et al were able to compare the rate of death between 10 days and the end of follow-up, and determined that the overall greatest risk of death is within the first week to 10 days. (6)

Composite outcome of mortality or dependency

Wardlaw et al also conducted an analysis to examine the composite outcome of mortality or dependency. There was a statistically significant reduction in mortality or dependency (OR 0.81, 95% CI 0.73 to 0.90, 9<0.0001). Wardlaw et al determined these results were largely weighted by the improvement in dependency over the long term compared to mortality in the short term. (6)

Conclusions

Mortality
Based on moderate quality of evidence, there was no difference in mortality among patients who received a recombinant tissue plasminogen (rt-Pa) activator as the thrombolytic agent compared to the control group.

Dependency
Based on moderate quality of evidence, there was a decrease in dependency among patients who received a thrombolytic agent compared to control group.

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
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Dr. Robert Teasell	Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine	Western University Lawson Research Institute St. Joseph's Health Care London
Dr. Paul E. Cooper	Senior Medical Director – Medicine, 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, Division of Critical Care	Quinte Health Care, Belleville Ontario
Dr. Moira Kapral	Division of General Internal Medicine & Clinical Epidemiology, Associate Professor, Department of Medicine, Scientist	University of Toronto Institute for Clinical Evaluative Sciences (ICES)
Dr. Murray Krahn	Director, THETA, F. Norman Hughes Chair and Professor, Department of Medicine and Faculty of Pharmacy	University of Toronto
Dr. Daniel Brouillard	Stroke Survivor/Internist	Kingston Heart Clinic
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		Centre
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Kathleen Lee	Social Worker	Health Sciences North
Linda Welham	Professional Resource, Case Costing and Decision Support	Southlake Regional Health Centre
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Thomas Smith	Acting Program Manager, Provincial Programs Branch	Ministry of Health and Long-Term Care

Appendices

Appendix 1: Literature Search Strategies

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: Study Details

Table A1: Details of Relevant RCTs in the Included Systematic Review[a]

Study Name, Year	Country	Inclusion Criteria		Intervention Details		Sample Size	Length of Follow-Up[b]
		Age	Stroke Type/ Severity	Thrombolytic Agent	Dose		
ASK 1996	Australia	18 – 85 yrs	Cortical and lacunar stroke	Streptokinase	1.5 MU	340	3 months
ATLANTIS A 2000	North America	18 – 79 yrs	All types	Tissue plasminogen activator	0.9 mg/kg body weight	142	3 months
ATLANTIS B 1999	North America	18 – 79 yrs	All types	Tissue plasminogen activator	0.9 mg/kg body weight	619	3 months
AUST 2005	Australia and New Zealand	18 – 85 yrs	Occlusion of internal carotid or middle cerebral or vertebra-basilar arteries	Urokinase[c]	100,000 IU increments	16	6 monts
Chen 2000	China	35 -75 yrs	Cortical and lacunar stroke	Urokinase	1.0 – 1.5 MU	465	3 months
DEDAS 2006	USA and Germany	18 – 85 yrs	Tissue at risk	Desmoteplase	90 – 125 µg/kg	37	1 month
DIAS 2005	12 countries	18 – 85 yrs	Tissue at risk	Desmoteplase	25mg – 125 µg /kg	104	3 months
DIAS 2 2008	Multiple sites	18 – 85 yrs	Tissue at risk	Desmoteplase	90 – 125 µg/kg	186	3 months
ECASS 1995	14 countries	18 – 80 yrs	hemispheric cortical ischemia	Tissue plasminogen activator	1.1 mg/kg	620	3 months
ECASS II 1998	Europe, Australia, New Zealand	18 – 80 yrs	hemispheric cortical ischemia	Tissue plasminogen activator	0.9 mg/kg	800	3 months
ECASS 3 2008	Europe	18 – 80 yrs	All types	Tissue plasminogen activator	0.9 mg/kg	821	3 months
EPITHET 2008	Australia, New Zealand, Belgium and UK	≥ 18yrs	hemispheric cortical ischemia	Tissue plasminogen activator	0.9 mg/kg	101	3 months
Haley 1993	USA	18 – 80 yrs	All types	Tissue plasminogen activator	0.85 mg/kg	27	3 months
MAST-E 1996	France and UK	> 18 yrs	hemispheric cortical ischemia	Streptokinase	1.5 MU	310	6 months
MAST-I 1995	Italy	> 18 yrs	All types	Streptokinase	1.5 MU	622	6 months
MELT 2007	Japan	20 – 75 yrs	Occlusion of internal carotid or middle cerebral artery	Urokinase[c]	600,000 IU	114	3 months
Morris 1995	UK	40 – 80 yrs	hemispheric cortical ischemia	Streptokinase	1.5 MU	20	3 months
NINDS 1995	USA	18 – 80 yrs[d]	All types	Tissue plasminogen activator	0.9 mg/kg	624	3 months
PROACT 1998	USA and Canada	18 85 yrs	Occlusion of internal carotid or middle cerebral artery	pro-Urokinase[c]	6 mg	40	3 months
PROACT 2 1999	USA and Canada	18 – 85 yrs	Occlusion of internal carotid or middle cerebral artery	pro-Urokinase[c]	9 mg	180	3 months
Wang 2003	China	35 – 80 yrs	All types	Tissue plasminogen activator	0.7 –5 0.9 mg/kg	100	3 months

Abbreviations: NIHSS, National Institute of Health Stroke Scale
[a] Wardlaw et al (6)
[b] converted to months (30 days =1 month)
[c] intra-arterial (all other are intravenous)
[d] upper age limit removed part way through study

Appendix 3: Quality Assessment Tables

Table A2: AMSTAR Score of 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
Mullen, 2012(3)	6	✓	✓	✓						✓	✓	✓
Warburton, 2011(7)	8	✓		✓	✓		✓	✓		✓	✓	✓
Wardlaw, 2009(6)	11	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] details of AMSTAR method are described in Shea et al (4)

Table A3: GRADE Evidence Profile for Comparison of Thrombolytics Versus Control Groups

No. of Studies (Design)	Risk of Bias[a]	Inconsistency	Indirectness[b]	Imprecision	Publication Bias	Upgrade Considerations	Quality
All cause mortality within 7 to 10 days							
12 (RCTs)	Serious limitations (-1)[a]	No serious limitations[c]	No serious limitations[b]	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Dependency							
17 (RCTs)	Serious limitations (-1)[a]	No serious limitations	No serious limitations[b]	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: No., number; RCT, randomized controlled trial.

[a] details outlined in Table A4. In summary: 3 studies stopped early for risk of harm; 5 studies had unclear allocation concealment; 1 study was stopped early for protocol change; 2 studies had data not available on all patients; 1 study analysis was active participants only and not intention-to-treat analysis; 2 studies had no allocation concealment; 1 study had no blinding; 1 study had a randomization error; 1 study had unclear blinding; and 1 study had a randomization method not stated

[b] Meta-analyses included all thrombolytics while in Ontario only rt-PA is approved for use, subgroup analyses were conducted as appropriate to manage this

[c] rt-PA subgroup analysis demonstrates some inconsistency in effect estimate

Table A4: Risk of Bias Among Randomized Controlled Trials for the Comparison of Thrombolytics versus Control Groups[a]

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
ASK 1996	No limitations	No limitations	Limitations[b]	None indicated	None indicated
ATLANTIS A 2000	Limitations[c]	No limitations	No limitations[d]	None indicated	None indicated
ATLANTIS B 1999	Limitations[c]	No limitations	Limitations[e]	None indicated	None indicated
Chen 2000	Limitations[c]	No limitations	Limitations[e]	None indicated	None indicated
DEDAS 2006	No limitations	No limitations	No limitations	None indicated	None indicated
DIAS 2005	No limitations	No limitations	No limitations	None indicated	None indicated
DIAS 2 2008	No limitations	No limitations	No limitations	None indicated	None indicated
ECASS 1995	No limitations	No limitations	No limitations	None indicated	None indicated
ECASS II 1998	No limitations	No limitations	No limitations	None indicated	None indicated
ECASS 3 2008	No limitations	No limitations	No limitations	None indicated	None indicated
EPITHET 2008	No limitations	No limitations	No limitations	None indicated	None indicated
Haley 1993	Limitations[c]	No limitations	Limitations[f]	None indicated	None indicated
MAST-E 1996	No limitations	No limitations	Limitations[b]	None indicated	None indicated
MAST-I 1995	Limitations[g]	Limitations[h]	Limitations[b]	None indicated	None indicated
Morris 1995	Limitations[c]	No limitations	No limitations	None indicated	None indicated
NINDS 1995	Limitations	No limitations	No limitations	None indicated	Limitations[i]
Wang 2003	Limitations[g]	Limitations[j]	No limitations	None indicated	Limitations[k]

[a] based on information abstracted from the systematic review by Wardlaw et al (6)
[b] stopped early for risk of harm
[c] unclear allocation concealment
[d] stopped early for protocol changed to ATLANTIS B
[e] data not available on all patients
[f] analysis was active participants only and not intention-to-treat analysis
[g] no allocation concealment
[h] no blinding, control group did not receive a placebo and it was a cross-over design
[i] randomization error for 13 – 31 patients
[j] unclear blinding
[k] randomization method not stated

Appendix 4: Supplementary Analyses

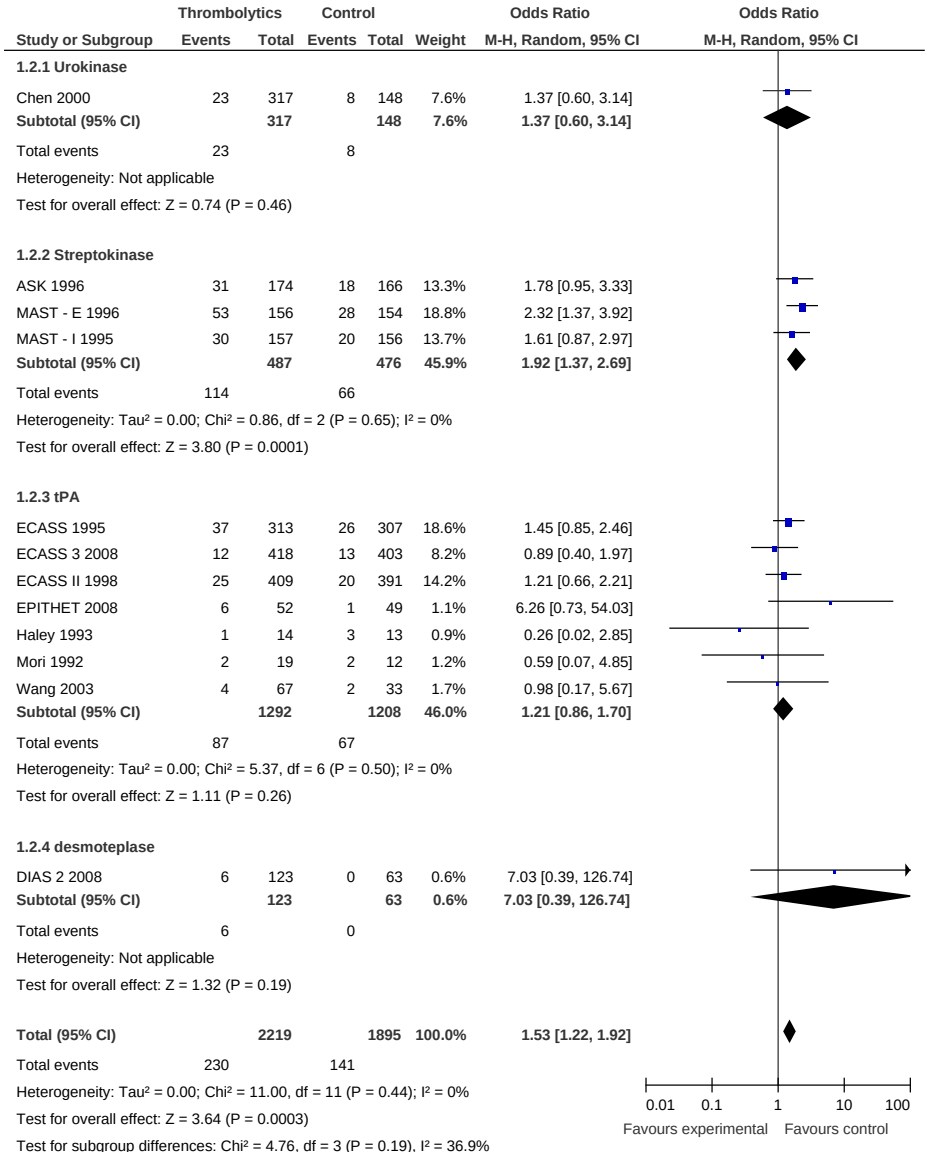

Figure 2: Effect Estimate of Mortality at 7 to 10 Days Use of a Thrombolytic Alone Compared to Control Group

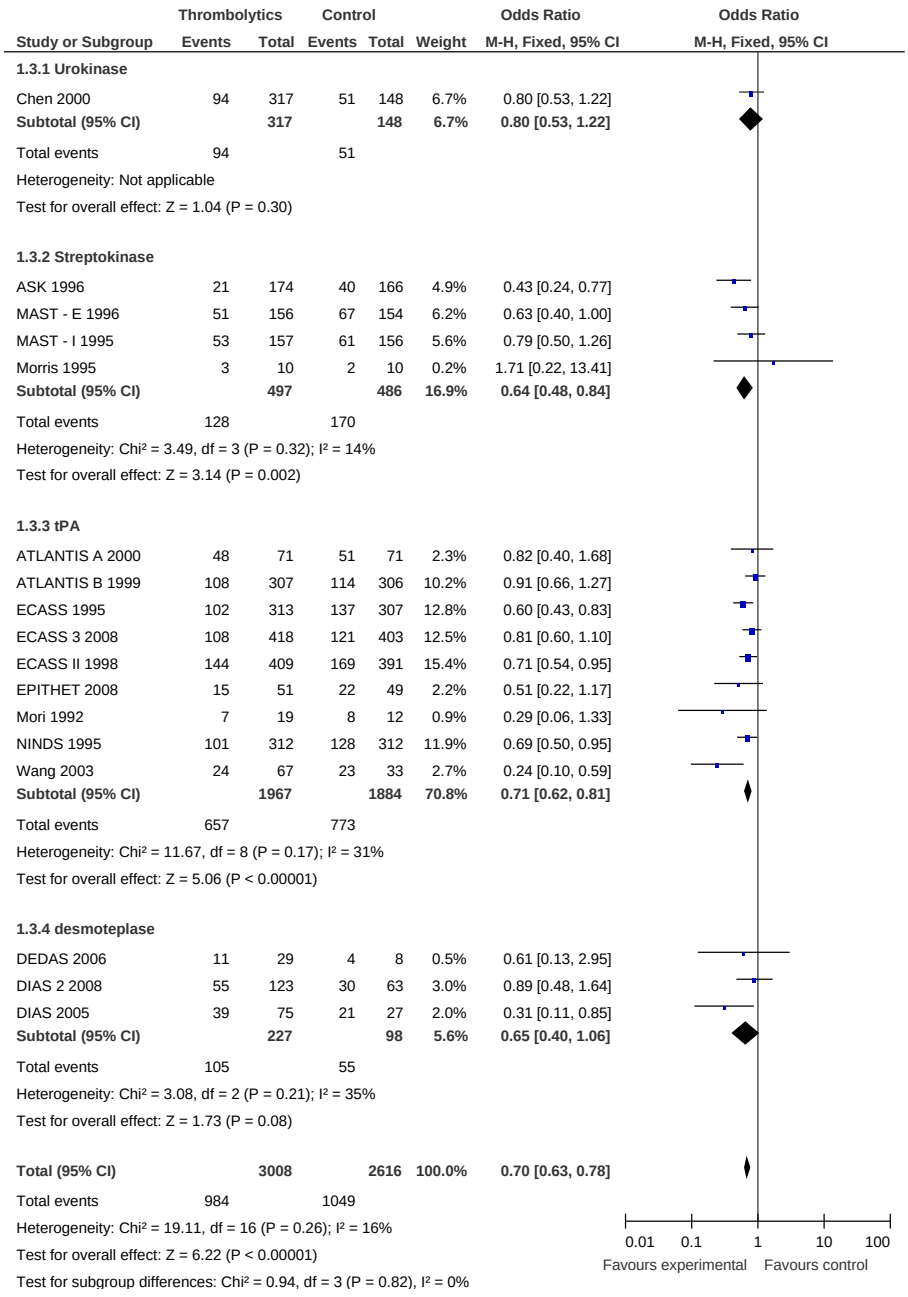

Figure 3: Effect Estimate of Dependency On Use of a Thrombolytic Alone Compared to Control Group

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