Appendices

Appendix I: Stroke Patient Group—ICD-10-CA Details

G45 **Transient cerebral ischaemic attacks and related syndromes**
Excludes:
Neonatal cerebral ischaemia (P91.0)

G45.0 **Vertebro-basilar artery syndrome**
G45.1 **Carotid artery syndrome (hemispheric)**
G45.2 **Multiple and bilateral precerebral artery syndromes**
G45.3 **Amaurosis fugax**
G45.8 **Other transient cerebral ischaemic attacks and related syndromes**
Includes:
Subclavian steal syndrome

G45.9 **Transient cerebral ischaemic attack, unspecified**
Includes:
Spasm of cerebral artery
Transient cerebral ischaemia NOS
Use additional code from category (E10-E14) with fourth and fifth digits .52 to classify any associated diabetes mellitus

I61 **Intracerebral haemorrhage**
Use additional code from category (E10-E14) with fourth and fifth digits .52 to classify any associated diabetes mellitus.

Excludes:
Sequelae of intracerebral haemorrhage (I69.1)

I61.0 Intracerebral haemorrhage in hemisphere, subcortical
Includes:
Deep intracerebral haemorrhage

I61.1 Intracerebral haemorrhage in hemisphere, cortical
Includes:
Cerebral lobe haemorrhage
Superficial intracerebral haemorrhage

I61.2 **Intracerebral haemorrhage in hemisphere, unspecified**
I61.3 **Intracerebral haemorrhage in brain stem**
I61.4 **Intracerebral haemorrhage in cerebellum**
I61.5 **Intracerebral haemorrhage, intraventricular**
I61.6 **Intracerebral haemorrhage, multiple localized**
I61.8 **Other intracerebral haemorrhage**

I61.9 **Intracerebral haemorrhage, unspecified**

I63 **Cerebral infarction**

Includes:

Occlusion and stenosis of cerebral and precerebral arteries, resulting in cerebral infarction

Use additional code from category (E10-E14) with fourth and fifth digits .52 to classify any associated diabetes mellitus

Excludes:

Sequelae of cerebral infarction (I69.3)

I63.0 **Cerebral infarction due to thrombosis of precerebral arteries**

I63.1 **Cerebral infarction due to embolism of precerebral arteries**

I63.2 **Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries**

I63.3 **Cerebral infarction due to thrombosis of cerebral arteries**

I63.4 **Cerebral infarction due to embolism of cerebral arteries**

I63.5 **Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries**

I63.8 **Other cerebral infarction**

I63.9 **Cerebral infarction, unspecified**

I64 **Stroke, not specified as haemorrhage or infarction**

Includes:

Cerebrovascular accident (CVA) NOS

Use additional code from category (E10-E14) with fourth and fifth digits .52 to classify any associated diabetes mellitus.

Excludes:

Sequelae of stroke (I69.4)

H34.1 **Central retinal artery occlusion**

Appendix II: Rapid Review Methodology

Table A1 and Figure A1 outline the process and components comprising the Evidence Development and Standards Branch Rapid Review process.

Table A1: Rapid Review Methodology

Steps	Components
1. Develop research question	Develop PICOS in consultation with experts, end users, applicant, etc. Limited scoping of question (e.g., Blue Cross Blue Shield, AETNA, CIGNA) Determine study selection criteria (inclusion/exclusion) Determine a maximum of 2 outcomes to GRADE in step 5
2. Conduct literature search	5 years English MEDLINE, EMBASE, Cochrane, Centre for Reviews and Dissemination SRs, MAs, HTAs (establish in advance that these study designs exist for your topic)
3. Screen and select studies	Selection of SRs, MAs, HTAs Rate SRs with AMSTAR Retrieve primary studies from SRs, MAs, HTAs for step 4
4. Conduct data extraction and analysis[a]	Extract data on 2 outcomes from primary studies
5. Apply GRADE assessment outcomes[a]	GRADE maximum of 2 outcomes
6. Write up findings	Write findings using Rapid Review template

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HTA, health technology assessment; MA, meta-analysis; PICOS, population, intervention, comparison, outcome, setting; SR, systematic review.

[a]These steps are required if the identified SRs, MAs, and/or HTAs did not use GRADE to assess relevant outcomes.

Appendix III: Rapid Reviews

Effectiveness of Increased Intensity of Rehabilitation in Post-Stroke Patients: A Rapid Review

S Sehatzadeh

January 2013

Suggested Citation

S Sehatzadeh. Effectiveness of increased intensity of rehabilitation in post-stroke patients: a rapid review. Toronto, ON: Health Quality Ontario; 2013 Jan. 24 p. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

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.

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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.

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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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Table of Contents

List of Abbreviations

FIM	Functional Independence Measure

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 investigate whether increasing the intensity of rehabilitation for the first few weeks after stroke can improve functional independency in terms of activities of daily living in patients with stroke.

Clinical Need and Target Population

Stroke is a leading cause of disability, and patients who have had a stroke often have long-term difficulties in performing activities of daily living such as personal care, sitting, or getting out of a chair. Rehabilitation helps stroke survivors regain skills that are lost when part of the brain is affected. It is a major part of patient care and can help to maximize physical function and independence.

In June 2012, the Expert Panel on Episode of Care for Stroke suggested that the Evidence Development and Standards unit of Health Quality Ontario (HQO) conduct a "rapid review" to provide the evidence for the effectiveness of 2 elements in stroke rehabilitation: the timing and the intensity of rehabilitation. The Expert Panel selected 2 measures, the Barthel Index of Activities of Daily Living and the Functional Independence Measure (FIM), to use in this rapid review.

Members of the Expert Panel included physicians specialized in physical medicine and rehabilitation, members of the Ontario Stoke Network, physicians treating stroke patients, experts from academic health economic centres, and personnel from the Ministry of Health and Long-Term Care. However, the statements, conclusions, and views expressed in this rapid review are the work of the Evidence Development and Standards unit of HQO and do not necessarily represent the views of members of the Stroke Expert Panel.

Rapid Review

Research Questions

Does increasing the intensity of rehabilitation enhance the motor and functional recovery of patients following stroke?

Do the observed benefits (if any) continue in the longer term if the intensive rehabilitation is removed?

Research Methods

Literature Search

A literature search was performed on May 23, 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, 2000, until May 23, 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

- studies published between January 1, 2000, and May 23, 2012
- studies compared 2 or more levels of intensity of rehabilitation
- randomized controlled trials (RCTs) and non-randomized trials
- English language full-text reports

Exclusion Criteria

- studies that compared 1 dose of therapy with no treatment
- studies in which experimental and control groups were not treated in the same setting
- studies that included patients with other neurological conditions (e.g., traumatic brain injury)
- studies that compared results between different centres
- studies in which therapy involved using drugs (e.g., vasoactive drugs, levodpa, botulinum toxin) in combination with physical therapy
- studies in which therapy involved using somatosensory stimulation
- studies that used constraint-induced movement therapy
- studies that used repetitive transcranial magnetic stimulation
- studies that used adjunctive therapy (e.g., acupuncture)
- studies on the treatment of contractures or shoulder pain following stroke

Outcomes of Interest

- Score on Barthel index or Functional Independence Measure (FIM)

Results of Literature Search

The database search yielded 1,713 citations published between January 1, 2000, and May 23, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. Systematic reviews and any major review article on the topic of intensity of rehabilitation were identified within the Reference Manager database. The full texts of these articles were reviewed to identify and compile a list of studies published since January 2000 for further assessment.

The literature search identified 3 systematic reviews, 1 evidence-based review, and 1 review of the guidelines on stroke rehabilitation (Table 1) From a list of studies included in these 5 citations, 8 studies that met the inclusion criteria were identified and included in this rapid review (Table 2). For each included study, the study design was identified and is summarized in Table 3, which is a modified version of a hierarchy of study design by Goodman. (1)

Table 1: Review Studies on Stroke Rehabilitation Identified Through Literature Search

Included Studies	Study Type	Design of Included Studies	Search Period	Objective
Veerbeek et al, 2011 (2)	Systematic review	RCTs	1990 to Oct 13, 2010	To determine the effects of augmented exercise therapy on gait, gait-related activities, and basic and extended ADL
Cooke et al, 2010 (3)	Systematic review	RCTs and quasi-RCTs	From induction of databases to Oct 2009	To determine the strength of current evidence for provision of a higher dose of the same types of exercise-based therapy to enhance motor recovery after stroke
Galvin et al, 2008 (4)	Systematic review	RCTs	From 1985 onward	To determine whether increased duration of exercise therapy is associated with improvement in ADL in stroke patients
Teasell et al, 2009 (5)	Evidence-based review	RCTs and non-RCTs	From 1980	To determine whether patients who receive post-stroke rehabilitation for longer period of time or at a higher level of intensity benefit more than those who receive conventional dosage of rehabilitation
Foley et al, 2012 (6)	Review of guidelines	Practice guidelines	N/A	To examine the related literature to determine whether a specific evidence-based recommendation could be supported

Abbreviations: ADL, activities of daily living; N/A, not applicable; RCT, randomized controlled trial.

Of the 8 studies identified, 7 used the Barthel Index as a measure of results and only 1 used the Functional Independence Measure (FIM); 5 provided mean scores with standard deviation (SD) and 3 provided median and interquartile ranges for the scores at the baseline and follow-up times.

Table 2: Studies on Stroke Rehabilitation Included in the Rapid Review

Study, Year	Study design Focus	Sample size, N Sample	Comparison Groups	Scale scores (Barthel or FIM) Mean (SD)
Askim et al, 2010 (7)	RCT Lower limb	62 Patients admitted to stroke unit with mild/moderate stroke within 14 days of stroke	**Intensive motor training (IMT) group**: received lower limb motor training in addition to standard treatment: 3 additional sessions of motor training/week for the first 4 weeks after discharge from the stroke unit, plus one additional session/week for the next 8 weeks. Each session was intended to be 30–50 minutes. Patients were also encouraged to receive home exercise training (10 repetitions of 4 tasks twice per day, 6 days/week) **Standard therapy (ST) group**: received 2 daily sessions of training focusing on ADL, 30 minutes, 5 days/week	**Barthel index** Baseline: IMT = 72.7 (20.0); ST = 70.8 (16.2) 4 weeks: IMT = 88 (NR); ST = 86.3 (NR) 12 weeks: IMT = 91.0 (NR); ST: 92.0 (NR) 26 weeks: IMT: 92.5 (9.7); ST: 91.4 (16.9); *P* = 0.48
GAPS, 2004 (8)	RCT Lower limb	70 Patients admitted to stroke rehabilitation facilities within 6 weeks of having stroke and able to tolerate and benefit from mobility rehabilitation	**Augmented PT group**: received double the amount of PT (60–80 minutes/day, 5 times/week), for a total of 34 hours (9 hours on lower limb, 10 hours on upper limb, 15 hours other work **Standard PT group**: received the regular amount of PT (30–40 minutes/day, 5 times/week, total of 21 hours (5 hours on lower limb, 5 hours on upper limb, 11 hours on other work)	**Barthel index** Baseline: Augmented PT = 11.8 (3.3); Standard PT = 10.3 (3.1) 4 weeks: Augmented PT = 14.6 (3.4); Standard PT = 14.1 (3.7); *P* = 0.55 3 months: Augmented PT = 16.6 (2.8); Standard PT = 16.1 (3.3); *P* = 0.39 6 months: Augmented PT = 16.9 (2.7); Standard treatment = 16.2 (4.2); *P* = 0.45
Sonoda et al, 2004 (9)	Non-RCT Gait and exercise related ADL	104 Patients admitted to hospital within 30–80 days of stroke	**Full-time integrated therapy (FIT)**: 40 minutes PT and 40 minutes OT/day for 7 days/week **Conventional therapy**: 40 minutes PT and 40 minutes OT/day for 5 days/week	**FIM scores** Baseline: FIT: 92.9 (15.9); Conventional: 95.3 (14.9); nonsignificant 6 weeks: FIT: 110.1 (12.1); Conventional: 106.9 (10.4); nonsignificant
Fang et al, 2003 (10)	RCT General	156 Patients admitted to stroke centre. Therapy started during the first week after stroke	**Additional early PT (AEP)**: 45 minutes, 5 days/week for 4 weeks, started first week after stroke **Routine therapy (RT)**: no professional rehabilitation therapy	**Modified Barthel index** Baseline: AEP = 25.70 (19.56); RT = 33.53 (31.04) 4 weeks: AEP = 47.67 (28.75); RT = 47.16 (28.73); nonsignificant 6 months: AEP = 83.93 (19.63); RT = 80.0 (32.96); nonsignificant
Di Lauro et al, 2003 (11)	Non-RCT General	60 Patients admitted to hospital with very severe stroke	**Intensive therapy**: 2 hours/day with an interval of 6 hours between the 2 hours, duration of 14 days **Ordinary therapy**: 45 minutes/day, duration of 14 days	**Barthel index** Baseline: intensive = 1.4 (1.4); ordinary = 1.5 (1.5) 2 weeks: intensive = 3.2 (2.0); ordinary = 3.2 (2.6) 6 months: intensive = 8.0 (2.8); ordinary = 7.7 (3.0); nonsignificant

Study, Year	Study design Focus	Sample size, N Sample	Comparison Groups	Scale scores (Barthel or FIM) Mean (SD)
Rodgers et al, 2003 (12)	RCT Upper limb	123 Patents admitted to stroke unit with upper limb dysfunction within 10 days of onset of stroke	**Enhanced upper limb rehabilitation (EUR) group**: 30 minutes per day/ 5 days a week of EUR for 6 weeks plus stroke unit care, median of 52 minutes/working day **Control group**: median of 38 minutes/ working day plus stroke unit care	**Barthel index** **Median (IQR)** Baseline: EUR = 8 (6–13); control = 9 (6–14); *P* = 0.7 3 months: EUR = 17 (8–19); control = 17 (10–19); *P* = 0.96 6 months: EUR: 18 (11–20);control: 17 (14–18); *P* = 0.28
Kwakkel et al, 2002 (13)	RCT	101 Severely disabled patients during the first 2 weeks after stroke admitted to hospital (Barthel index of 9 or lower)	**Arm training group**: received arm training for 30 minutes per day/ 5 days per week for 20 weeks **Leg training group**: received leg training for 30 minutes per day/ 5 days per week for 20 weeks **Control group**: arm and leg were immobilized for 30 minutes, 5 days per week, 20 weeks All 3 groups received 15 minutes of lower limb rehabilitation, 15 minutes of upper limb rehabilitation, and 1.5 hour of ADL training	**Barthel index** **Median (IQR)** Baseline: arm training = 5 (3–7); leg training = 6 (3–8); control = 5.5 (3–7) 6 weeks: arm training = 10 (5–13); leg training = 13 (8.8–19.0); immobilized = 8.5 (7–13); arm vs. leg training = *P* < 0.01 12 weeks: arm training = 14 (10.8–18); leg training = 17 (13–20); immobilized = 11 (8–18); leg training vs. immobilized = *P* < 0.05 20 weeks: arm training = 17 (14.3–20); leg training = 19 (16–20); immobilized = 16 (10–19); leg training vs. immobilized = *P* < 0.05 for difference between leg training and immobilized 26 weeks: arm training = 17 (11.8–20); leg training = 19 (15–20); control = 17 (10.5–19); nonsignificant 38 weeks: arm training = 17 (10.5–20); leg training = 17.5 (15.25–20.0); control = 17 (12.5–18.25); nonsignificant 1 year: arm training = 15 (12.5–20); leg training = 18 (14.5–20); control = 17 (14–20); nonsignificant
Gilbertson et al, 2000 (14)	RCT	138 Patients admitted to hospital with a definite plan for discharge from hospital (median days after stroke 23–31 days)	**Domiciliary OT group**: for 6 weeks **Routine follow-up group**: receive routine services	**Barthel index** **Median (IQR)** Baseline: domiciliary OT = 17 (15–18); routine = 18 (16–19) 8 weeks: domiciliary OT = 18 (16–20); routine: 17 (14–19); *P* = 0.06 6 months: domiciliary OT = 17 (15–19); routine: 17 (13–18); *P* = 0.25

Abbreviations: AEP, additional early physiotherapy; ADL, activities of daily living; EUR, enhanced upper limb rehabilitation; FIM, Functional Independence Measure; FIT, full time integrated treatment; IMT, intensive motor training; IQR, interquartile range; NR, not reported; OT, occupational therapy; PT physiotherapy; RCT, randomized controlled trial; RT, routine therapy; ST, standard therapy.

Table 3: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	6
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	2
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**8**

Abbreviation: RCT, randomized controlled trial.

Results from 4 studies that reported the mean and SD (7;8;10;11) were used for pooling data and providing a summary effect size for the intervention under the study. Figure 1 shows the effect size with respect to improvement in Barthel Index 2 to 6 weeks after intensive rehabilitation. The improvement in each study was minimal and nonsignificant and the summary effect size was also nonsignificant (see Figure 1). A result from 1 study in which the FIM was reported was consistent with this finding. There was no significant difference between the intensive and the standard groups at the 6-week follow-up (Table 3).

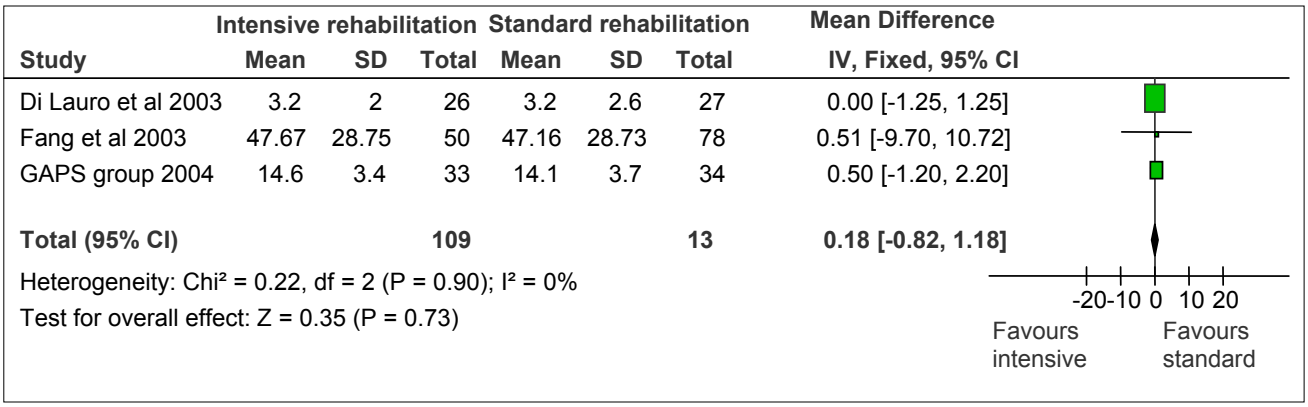

Figure 1: Comparison Between Intensive Rehabilitation and Standard Rehabilitation: Mean Barthel Index Scores at 2–6 Weeks Postintervention

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation,

All 4 studies that reported the mean scores for Barthel Index at 6 months reported a minimal and nonsignificant improvement in scores. The pooled summary effect size and 95% confidence interval (CI) was 0.53 (95% CI: −0.65 to 1.70) indicating no significant improvement. In addition, the confidence intervals for summary effect size included negative scores (Figure 2). The effect of higher intensity of rehabilitation on the Barthel Index appeared to be no greater than that of standard physiotherapy.

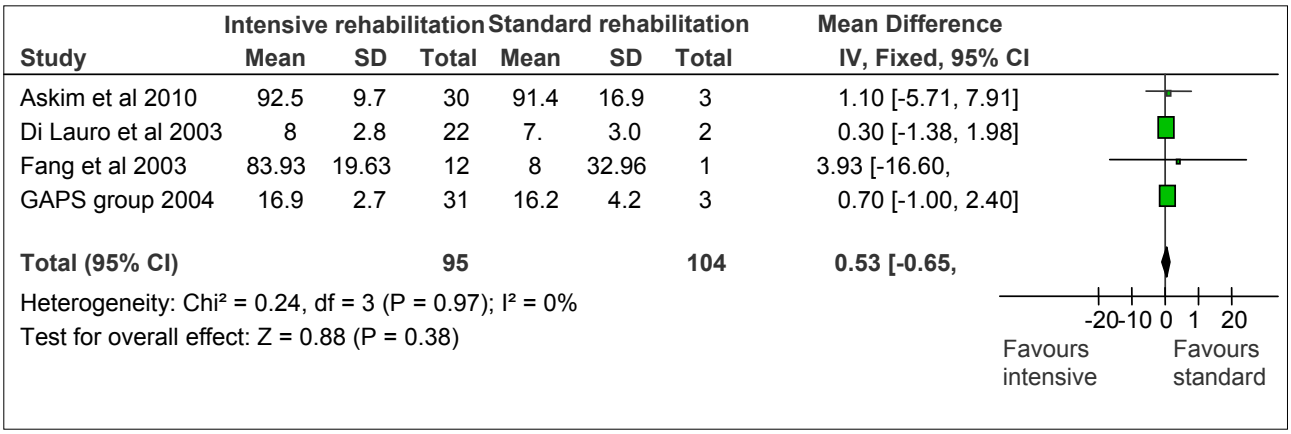

Figure 2: Comparison Between Intensive Rehabilitation and Standard Rehabilitation: Mean Barthel Index Scores at 6 Months Postintervention

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.

Results from 3 studies (12-14) on hospitalized patients that reported the median scores are consistent with the pooled summary effect size drawn from the mean scores. None of these studies found a significant difference between intensive therapy and standard therapy groups at different time points (see Table 3).

When the scores at baseline and at 6 months after the start of therapy were compared, a significant improvement was observed for both the intensive therapy group and the standard therapy group (see Figures 3–4). (7;8;10;11)

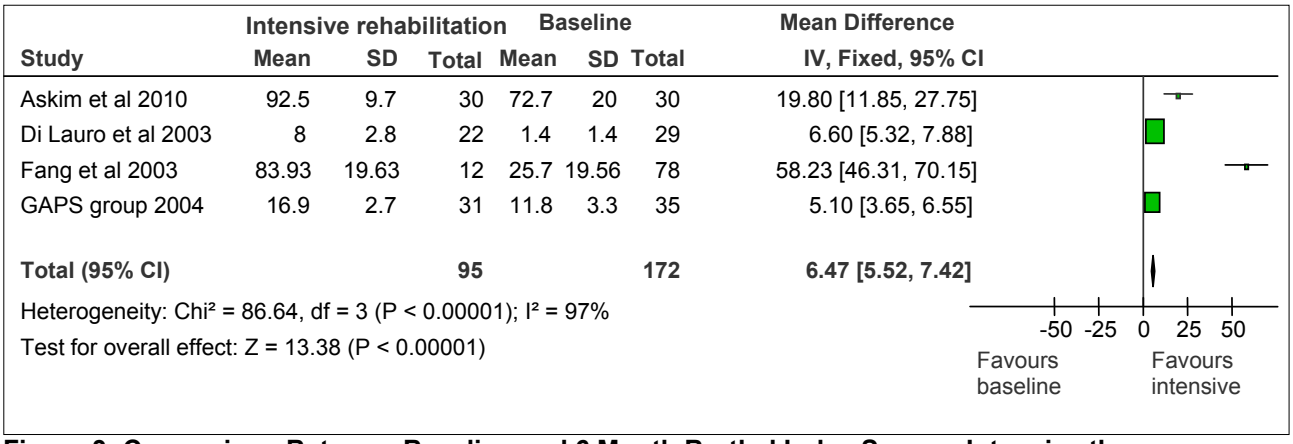

Figure 3: Comparison Between Baseline and 6 Month Barthel Index Scores: Intensive therapy Group

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation,

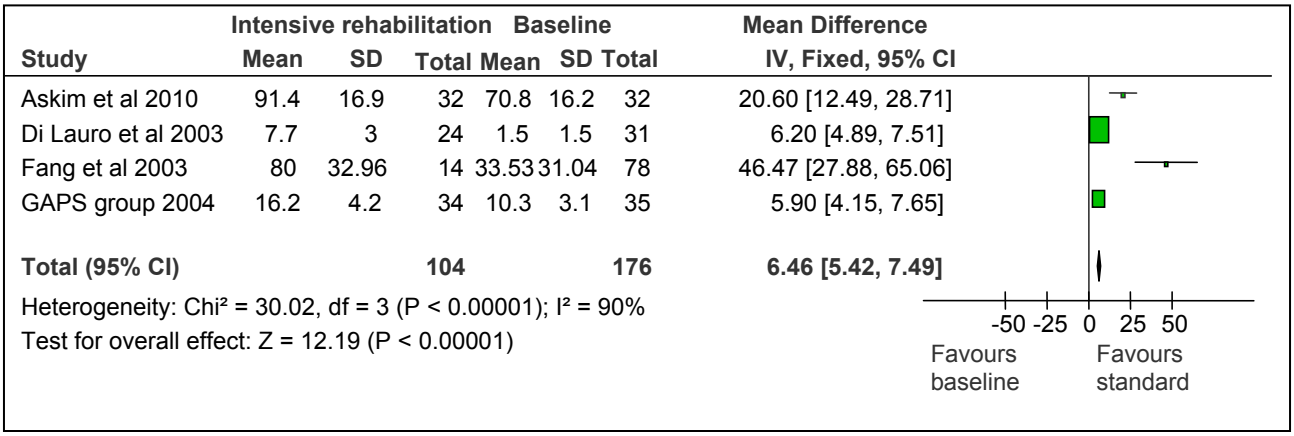

Figure 4: Comparison Between Baseline and 6 Month Barthel Index Scores: Standard Therapy Group

Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.

Conclusions

The majority of the studies analyzed were randomized controlled trials (RCTs) and included patients hospitalized for stroke. These studies compared 1 level of intensity of rehabilitation with another. The summary score of the studies that reported mean scores as well as the results of individual studies are consistent. In conclusion, the present finding suggests that functional recovery in patients hospitalized for stroke, as measured using the Barthel Index or Functional Independence Measure (FIM) scores, is not greater with higher intensity rehabilitation compared with the standard rehabilitation.

Significant improvements in scores from baseline to 6 months were observed regardless of the intensity of rehabilitation. This improvement may also be due to spontaneous natural neurological recovery or through other interventions that may enhance neurological recovery.

Acknowledgements

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Appendices

Appendix 1: Literature Search Strategies

Stroke Mega – Timing and Intensity – With Filter

Search date: May 23, 2012
Databases searched: OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, EBSCO CINAHL, Centre for Reviews and Dissemination.

Database: Ovid MEDLINE(R) <1946 to May Week 2 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 22, 2012>, Embase <1980 to 2012 Week 20>
Search Strategy:
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1 exp Stroke/ or exp brain ischemia/ (287672)
2 exp intracranial hemorrhages/ use mesz (50432)
3 exp brain hemorrhage/ use emez (71088)
4 exp stroke patient/ use emez (6013)
5 (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab. (338097)
6 or/1-5 (534080)
7 exp Rehabilitation/ or exp Rehabilitation Nursing/ (316326)
8 exp Rehabilitation Centers/ use mesz (11013)
9 exp rehabilitation center/ use emez (7721)
10 exp rehabilitation medicine/ or exp rehabilitation research/ use emez (4409)
11 exp rehabilitation care/ use emez (6660)
12 exp Stroke/rh [Rehabilitation] (12051)
13 exp Physical Therapy Modalities/ use mesz (111074)
14 exp physical medicine/ use emez (342325)
15 exp mobilization/ use emez (13653)
16 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*).ti,ab. (713739)
17 or/7-16 (1294415)
18 exp Time/ or exp early diagnosis/ (1590332)
19 exp Early Ambulation/ use mesz (1743)
20 exp dose response/ use emez (325509)
21 exp early intervention/ use emez (6066)
22 exp treatment duration/ or exp exercise intensity/ use emez (74351)
23 ((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) adj4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)).ti,ab. (85222)
24 or/18-23 (2049040)
25 6 and 17 and 24 (7419)
26 limit 25 to english language (6427)

27 limit 26 to yr="2000 -Current" (4692)
28 limit 27 to (controlled clinical trial or meta analysis or randomized controlled trial) (941)
29 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ use mesz (65937)
30 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ use emez (564879)
31 (health technology adj2 assess$).ti,ab. (3344)
32 exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/ use mesz (395178)
33 Randomized Controlled Trial/ or exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/ use emez (948468)
34 (random* or RCT).ti,ab. (1323538)
35 (placebo* or sham*).ti,ab. (432668)
36 (control* adj2 clinical trial*).ti,ab. (36879)
37 meta analysis/ use emez (62925)
38 (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. (272913)
39 or/28-38 (2279091)
40 27 and 39 (1648)
41 remove duplicates from 40 (1254)

CINAHL

#	Query	Results
S22	S18 and S21	310
S21	S19 or S20	161778
S20	random* or sham*or rct* or health technology N2 assess* or meta analy* or metaanaly* or pooled analysis or (systematic* N2 review*) or published studies or medline or embase or data synthesis or data extraction or cochrane or control* N2 clinical trial*	153534
S19	(MH "Random Assignment") or (MH "Random Sample+") or (MH "Meta Analysis") or (MH "Systematic Review") or (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies") or (MH "Placebos") or (MH "Control (Research)")	86447
S18	S13 and S10 and S17 Limiters - Published Date from: 20000101-20121231; English Language	1257
S17	S11 or S12 or S13 or S14 or S15 or S16	84030
S16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) N4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	11949
S15	(MH "Exercise Intensity")	4976
S14	(MH "Treatment Duration") OR (MH "Treatment Delay")	4575
S13	(MH "Dose-Response Relationship")	1683
S12	(MH "Early Ambulation") OR (MH "Early Intervention+")	7173
S11	(MH "Time+")	61875
S10	S12 or S11 or S10	227197
S9	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis*	186687

	or occupational therap* or mobilization or mobilisation or strength train*)	
S8	(MH "Rehabilitation Nursing") or (MH "Stroke/RH")	7715
S7	(MH "Rehabilitation+") OR (MH "Rehabilitation Centers+") OR (MH "Rehabilitation Patients")	127293
S6	S18 OR S17 OR S16 OR S15 OR S14	44368
S5	(MH "Stroke Patients")	1905
S4	stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain N2 isch?emia or cerebral N2 isch?emia or intracranial N2 hemorrhag* or brain N2 hemorrhag*	39784
S3	(MH "Intracranial Hemorrhage+")	4778
S2	(MH "Cerebral Ischemia+")	5531
S1	(MH "Stroke")	25810

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	671
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES	180
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES	144
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))	2188
5	#1 OR #2 OR #3 OR #4	2292
6	MeSH DESCRIPTOR Rehabilitation EXPLODE ALL TREES	1323
7	MeSH DESCRIPTOR Rehabilitation Nursing EXPLODE ALL TREES	7
8	MeSH DESCRIPTOR Rehabilitation Centers EXPLODE ALL TREES	70
9	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES WITH QUALIFIER RH	134
10	MeSH DESCRIPTOR Physical Therapy Modalities EXPLODE ALL TREES	1527
11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)	6719
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	7525
13	MeSH DESCRIPTOR time EXPLODE ALL TREES	1822
14	MeSH DESCRIPTOR Early Ambulation EXPLODE ALL TREES	22
15	MeSH DESCRIPTOR Early diagnosis EXPLODE ALL TREES	156
16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) adj4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	578
17	#13 OR #14 OR #15 OR #16	2527

18	#5 AND #12 AND #17	103
19	(#5 AND #12 AND #17) FROM 2000 TO 2012	88

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor **Stroke** explode all trees	4025
#2	MeSH descriptor **Brain Ischemia** explode all trees	1936
#3	MeSH descriptor **Intracranial Hemorrhages** explode all trees	1116
#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	16313
#5	(#1 OR #2 OR #3 OR #4)	18009
#6	MeSH descriptor **Rehabilitation** explode all trees	11919
#7	MeSH descriptor **Rehabilitation Nursing** explode all trees	32
#8	MeSH descriptor **Rehabilitation Centers** explode all trees	503
#9	MeSH descriptor **Stroke** explode all trees with qualifier: **RH**	1014
#10	MeSH descriptor **Physical Therapy Modalities** explode all trees	12459
#11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)	74282
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	80911
#13	MeSH descriptor **Time** explode all trees	48228
#14	MeSH descriptor **Early Diagnosis** explode all trees	490
#15	MeSH descriptor **Early Ambulation** explode all trees	257
#16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) NEAR/4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	16018
#17	(#13 OR #14 OR #15 OR #16)	62212
#18	(**#5** AND **#12** AND **#17**), from 2000 to 2012	840

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

S Brener

January 2013

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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.

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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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Table of Contents

List of Abbreviations

CI	Confidence interval
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).

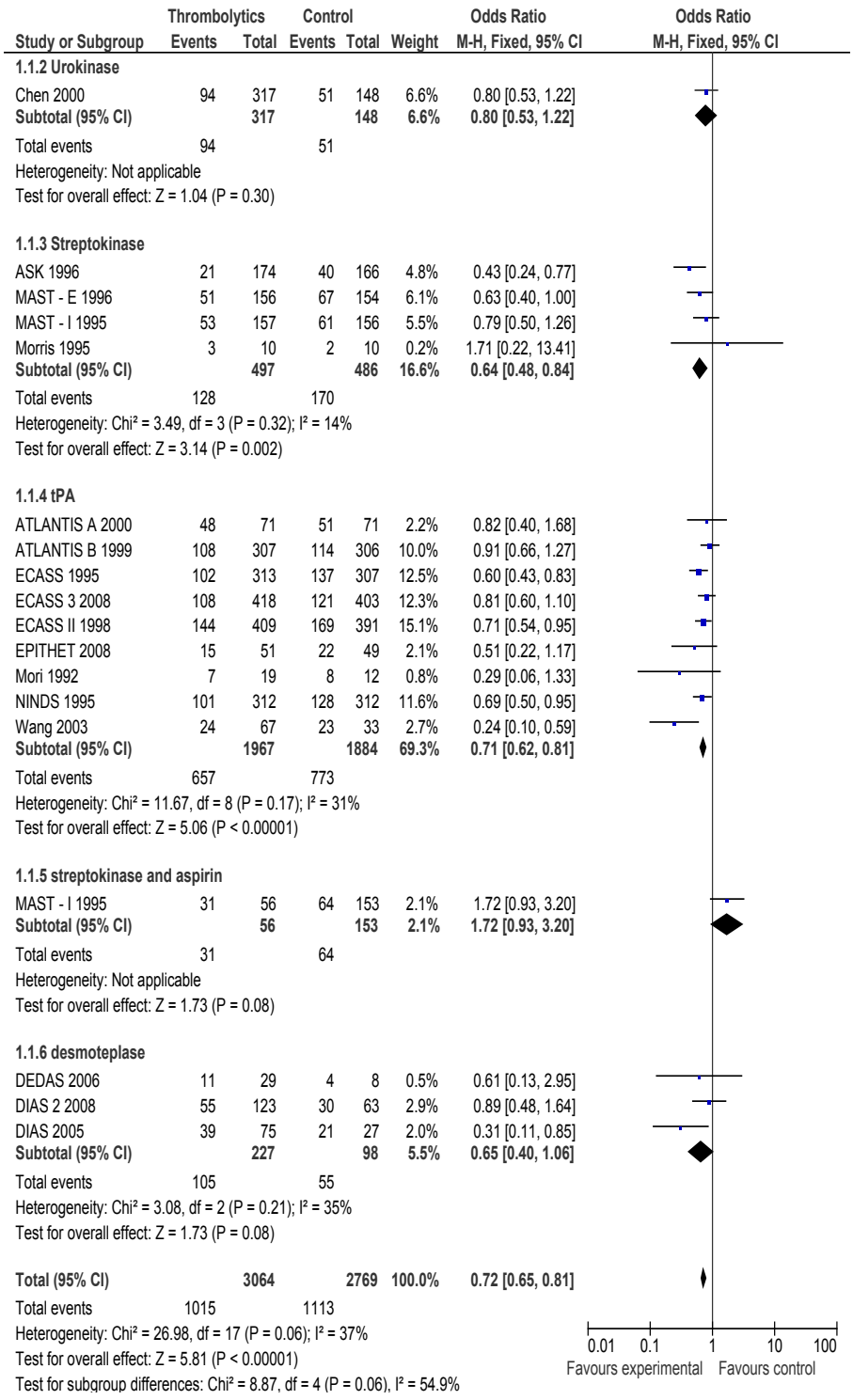

Figure 1: Forest Plot of Impact of Intravenous Thrombolytics on Dependency

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 Dr. R. Loch MacDonald	Internist / Stroke Survivor Keenan Endowed Chair in Surgery Head, Division of Neurosurgery, Professor of Surgery, University of Toronto	Kingston Heart Clinic St. Michael's Hospital
Dr. Ruth Hall	OSN Evaluation Lead and Adjunct Scientist	Ontario Stroke Network, Institute for Clinical Evaluative Sciences
Linda Kelloway	Best Practices Leader	Ontario Stroke Network
Rhonda Whiteman	Clinical Nurse Specialist, Stroke Best Practice Coordinator	Hamilton Health Sciences Centre
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Deborah Willems	Regional Rehabilitation Coordinator, Southwestern Ontario Stroke Network	London Health Sciences Centre
Holly Sloan	Speech-Language Pathologist	Trillium Health Centre Site, Credit Valley Hospital and Trillium Health Centre

Name	Role	Organization
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Kathleen Lee	Social Worker	Health Sciences North
Linda Welham	Professional Resource, Case Costing and Decision Support	Southlake Regional Health Centre
Lori Marshall	Executive Vice President, Strategy, Performance and Aboriginal Health	Thunder Bay Regional Health Sciences Centre
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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:

#	Searches	Results
1	exp Stroke/ or exp brain ischemia/	303136
2	exp intracranial hemorrhages/ use mesz	51691
3	exp brain hemorrhage/ use emez	74542
4	exp stroke patient/ use emez	6733
5	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab.	356017
6	or/1-5	558642
7	exp Thrombolytic Therapy/ use mesz	17601
8	exp Tissue Plasminogen Activator/ use mesz	14277
9	exp fibrinolytic agent/ use emez	94175
10	exp plasminogen activator/ use emez	59867
11	(thromboly* or fibrinoly*).ti,ab.	115138
12	(plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).ti,ab.	115580
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.	43280
14	or/7-13	250061
15	6 and 14	29996
16	limit 15 to english language	26562
17	limit 16 to yr="2008 -Current"	12592
18	Meta Analysis.pt.	37256
19	Meta Analysis/ use emez	66936
20	Systematic Review/ use emez	54406
21	exp Technology Assessment, Biomedical/ use mesz	8883
22	Biomedical Technology Assessment/ use emez	11409
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.	295627
24	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3811
25	or/18-24	355683
26	17 and 25	653
27	remove duplicates from 26	458

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Stroke] explode all trees	4121
#2	MeSH descriptor: [Brain Ischemia] explode all trees	1967
#3	MeSH descriptor: [Intracranial Hemorrhages] explode all trees	1133
#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	16432
#5	#1 or #2 or #3 or #4	18151
#6	MeSH descriptor: [Thrombolytic Therapy] explode all trees	1551
#7	MeSH descriptor: [Tissue Plasminogen Activator] explode all trees	1282
#8	thromboly* or fibrinoly*:ti,ab,kw (Word variations have been searched)	6326
#9	plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA:ti,ab,kw (Word variations have been searched)	3683
#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)	2194
#11	#6 or #7 or #8 or #9 or #10	8091
#12	#5 and #11 from 2008 to 2012	362
#13	#12 in Trials	288
#14	#12 not #13	74

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	706
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES	189
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES	146
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))	2327
5	#1 OR #2 OR #3 OR #4	2431
6	MeSH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES	178
7	MeSH DESCRIPTOR Tissue Plasminogen Activator EXPLODE ALL TREES	72
8	(thromboly* or fibrinoly*)	530
9	(plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA)	171
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)	149
11	#6 OR #7 OR #8 OR #9 OR #10	580
12	#5 AND #11	236
13	(#12) FROM 2008 TO 2012	93

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

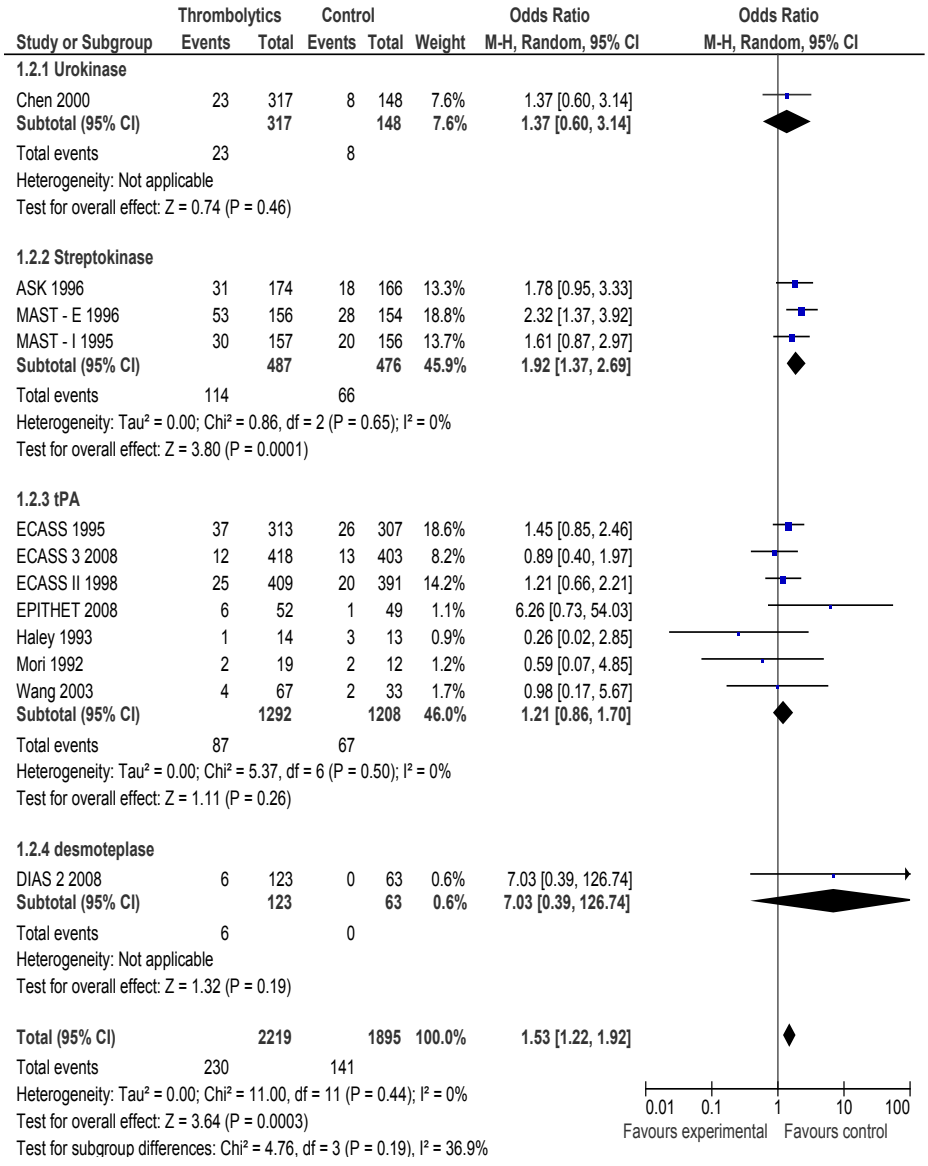

Figure 2: Effect Estimate of Mortality at 7 to 10 Days Use of a Thrombolytic Alone Compared to Control Group

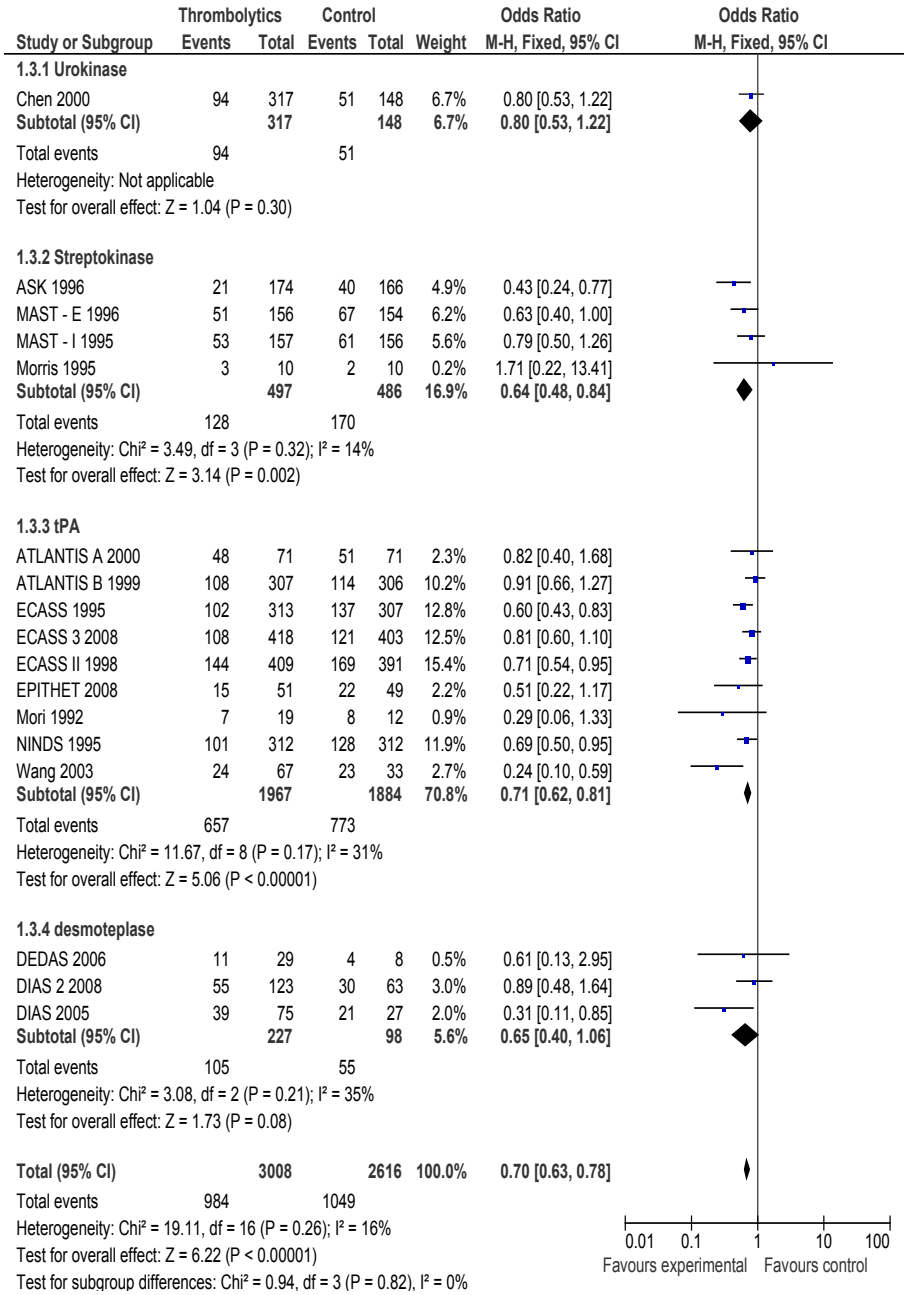

Figure 3: Effect Estimate of Dependency On Use of a Thrombolytic Alone Compared to Control Group

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Optimized Timing of Thrombolytic Therapy for the Treatment of 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.

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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.

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Table of Contents

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.

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Dr. Paul E. Cooper	Senior Medical Director – Medicine, Chief, Department of Clinical Neurological Sciences	London Health Sciences Centre
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Dr. Murray Krahn	Director, THETA, F. Norman Hughes Chair and Professor, Department of Medicine and Faculty of Pharmacy	University of Toronto
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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:

#	Searches	Results
1	exp Stroke/ or exp brain ischemia/	303136
2	exp intracranial hemorrhages/ use mesz	51691
3	exp brain hemorrhage/ use emez	74542
4	exp stroke patient/ use emez	6733
5	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab.	356017
6	or/1-5	558642
7	exp Thrombolytic Therapy/ use mesz	17601
8	exp Tissue Plasminogen Activator/ use mesz	14277
9	exp fibrinolytic agent/ use emez	94175
10	exp plasminogen activator/ use emez	59867
11	(thromboly* or fibrinoly*).ti,ab.	115138
12	(plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).ti,ab.	115580
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.	43280
14	or/7-13	250061
15	6 and 14	29996
16	limit 15 to english language	26562
17	limit 16 to yr="2008 -Current"	12592
18	Meta Analysis.pt.	37256
19	Meta Analysis/ use emez	66936
20	Systematic Review/ use emez	54406
21	exp Technology Assessment, Biomedical/ use mesz	8883
22	Biomedical Technology Assessment/ use emez	11409
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.	295627
24	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3811
25	or/18-24	355683
26	17 and 25	653
27	remove duplicates from 26	458

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Stroke] explode all trees	4121
#2	MeSH descriptor: [Brain Ischemia] explode all trees	1967
#3	MeSH descriptor: [Intracranial Hemorrhages] explode all trees	1133
#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	16432
#5	#1 or #2 or #3 or #4	18151
#6	MeSH descriptor: [Thrombolytic Therapy] explode all trees	1551
#7	MeSH descriptor: [Tissue Plasminogen Activator] explode all trees	1282
#8	thromboly* or fibrinoly*:ti,ab,kw (Word variations have been searched)	6326
#9	plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA:ti,ab,kw (Word variations have been searched)	3683
#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)	2194
#11	#6 or #7 or #8 or #9 or #10	8091
#12	#5 and #11 from 2008 to 2012	362
#13	#12 in Trials	288
#14	#12 not #13	74

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	706
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES	189
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES	146
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))	2327
5	#1 OR #2 OR #3 OR #4	2431
6	MeSH DESCRIPTOR Thrombolytic Therapy EXPLODE ALL TREES	178
7	MeSH DESCRIPTOR Tissue Plasminogen Activator EXPLODE ALL TREES	72
8	(thromboly* or fibrinoly*)	530
9	(plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA)	171
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)	149
11	#6 OR #7 OR #8 OR #9 OR #10	580
12	#5 AND #11	236
13	(#12) FROM 2008 TO 2012	93

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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Relationship of Patient Volume and Stroke Outcomes: A Rapid Review

D Ling

January 2013

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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

HQO	Health Quality Ontario
RCT	Randomized controlled trial

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 investigate whether there is a minimum or appropriate annual patient volume that optimizes clinical outcomes in stroke patients.

Clinical Need and Target Population

Stroke is a leading cause of death and disability. (1;2) The relationship between higher patient volume and better clinical outcomes has been established for several medical conditions and interventions, (3) but this association has not been adequately assessed for stroke. In addition, if a positive volume to outcome relationship exists, it is important to determine the critical mass volume that is required in hospitals to optimize outcomes for stroke patients.

Rapid Review

Research Question

What is the minimum or appropriate number of stroke patients that need to be treated in hospitals in 1 year to optimize clinical outcomes?

Research Methods

Literature Search

A literature search was performed October 31, 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 October 31, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained.

Inclusion Criteria

- English language full-reports
- published between January 1, 2008, and October 31, 2012
- health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and guidelines

Exclusion Criteria

- studies where quantitative results on stroke patient volume cannot be abstracted
- studies that did not assess the outcomes of interest

Outcomes of Interest

- Mortality
- Readmission
- Length of hospital stay
- Quality of life
- Institutionalization
- Dependency

Expert Panel

In October 2012, an Expert Advisory Panel on Stroke was struck. Members of the expert panel included physicians specialized in physical medicine and rehabilitation, members of the Ontario Stoke Network, physicians treating stroke patients, experts from academic health economic centres, and personnel from the Ministry of Health and Long-Term Care.

The Expert Advisory Panel on stroke suggested that the Evidence Development and Standards unit of Health Quality Ontario (HQO) conduct a "Rapid Review" to provide the evidence for the relationship between annual hospital volume and clinical outcomes for stroke patients. 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 quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (4) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology. Only published articles were evaluated for quality.

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. (4) For more detailed information, please refer to the latest series of GRADE articles. (4)

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 770 citations published between January 1, 2008, and October 31, 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.

One study (1 conference abstract) met the inclusion criteria. Three additional citations (2 observational studies and 1 conference abstract) were found through an initial scoping review in a non-systematic fashion and were included for a total of 4 included citations.

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (5)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	2
Case series	
Retrospective review, modelling	
Studies presented at an international conference	2
Expert opinion	
Total	4

Abbreviation: RCT, randomized controlled trial.

Table 2: Studies Included in the Rapid Review

Author, Year	Country	Study Design	Sample Size	Outcomes
Saposnik et al, 2007 (6)	Canada	Retrospective population-based study	26,676	In-hospital mortality (7-day and at discharge) after ischemic stroke
Svendsen et al, 2012 (7)	Denmark	Retrospective population-based study	63,995	Mortality after 30 days or 1 year; length of stay from admission to death or discharge; Hospital readmission after 1 year for all causes
Alvarez-Sabin et al, 2010 (8)	Spain	Observational cohort study	1297	Mortality and disability at discharge in hospitals without stroke units
Hall et al, 2012 (9)	Canada	Retrospective population-based study	71,856	All-cause mortality after 30 days

Table 3: Results of Studies Included in the Rapid Review

Author, Year	Objective	Study Design and Methods	Results	Limitations
Saposnik et al, 2007 (6)	To determine whether annual stroke volume is associated with in-hospital mortality after ischemic stroke	Retrospective study using administrative health data	Reduced mortality (7-day and at discharge) in high-volume facilities (> 100 patients/year) versus low-volume facilities (< 50 patients/year)	Administrative health data lack information on stroke severity and clinical factors to adjust for case mix
Svendsen et al, 2012 (7)	To examine whether annual stroke volume is associated with 30-day and 1-year mortality, length of hospital stay, and readmission in 1 year	Retrospective study using administrative health data	Higher annual volume was associated with reduced length of stay and 1-year hospital readmission; no association was found between volume and mortality	Non-randomized design cannot exclude presence of residual or unmeasured confounding
Alvarez-Sabin et al, 2010 (8)	To determine if annual stroke volume influences patient outcomes	Observational cohort study of consecutive stroke patients	Low annual stoke volume (< 300 patients) was independently associated with mortality and disability at discharge	Non-randomized design; only hospitals without stroke units
Hall et al, 2012 (9)	To examine the relationship between volume and 30-day mortality among ischemic stroke patients	Retrospective study using administrative health data	Low-volume hospitals (15–120 patients/year) have a 26% higher mortality rate than high-volume (201–456 patients/year) hospitals; no difference was found between high-volume and medium-volume hospitals	Administrative health data lack information to adjust for all potential confounding or bias

Conclusions

There is low-quality evidence that higher hospital volume is associated with fewer adverse outcomes in stroke patients.

There is a lack of evidence on the minimum or appropriate annual number of stroke patients required to optimize clinical outcomes.

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

Name	Role	Organization
Dr. Mark Bayley	Medical Director, Brain and Spinal Cord Rehab Program	UHN Toronto Rehab and Department of Medicine, University of Toronto
Ms. Christina O'Callaghan	Executive Director	Ontario Stroke Network
Dr. Gustavo Saposnik	Director, Stroke Outcomes Research Centre, Associate Professor of Medicine, Division of Neurology, St. Michael's Hospital	Institute for Clinical Evaluative Sciences, University of Toronto
Dr. Richard Swartz	Director, University of Toronto Stroke Program Medical Director, NE-GTA Regional Stroke Program, Associate Professor, Division of Neurology, Department of Medicine	Sunnybrook Health Sciences Centre, University of Toronto
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 Dr. R. Loch MacDonald	Internist / Stroke Survivor Keenan Endowed Chair in Surgery Head, Division of Neurosurgery, Professor of Surgery, University of Toronto	Kingston Heart Clinic St. Michael's Hospital
Dr. Ruth Hall	OSN Evaluation Lead and Adjunct Scientist	Ontario Stroke Network, Institute for Clinical Evaluative Sciences
Linda Kelloway	Best Practices Leader	Ontario Stroke Network
Rhonda Whiteman	Clinical Nurse Specialist, Stroke Best Practice Coordinator	Hamilton Health Sciences Centre
Rebecca Fleck	Occupational Therapist, Regional Stroke Education and Research Coordinator, Central South Regional Stroke Network	Hamilton Health Sciences Centre
Deborah Willems	Regional Rehabilitation Coordinator, Southwestern Ontario Stroke Network	London Health Sciences Centre
Holly Sloan	Speech-Language Pathologist	Trillium Health Centre Site, Credit Valley Hospital and Trillium Health Centre

Name	Role	Organization
Matthew Meyer	Research Coordinator, PhD Candidate, Epidemiology and Biostatistics	OSN & Lawson Health Research Institute, Schulich School of Medicine and Dentistry, Western University
Kathleen Lee	Social Worker	Health Sciences North
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Lori Marshall	Executive Vice President, Strategy, Performance and Aboriginal Health	Thunder Bay Regional Health Sciences Centre
Jin-Hyeun Huh	Pharmacy Director of Inpatient Operations, Department of Pharmacy	University Health Network
Derek Leong	Clinical Pharmacist, General Internal Medicine	University Health Network – Toronto General Hospital
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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

Literature Search – Stroke Rapid Review – Patient Volumes

Search date: October 31, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; CINAHL; Cochrane Library; CRD

Q: What is the minimum or appropriate number of stroke patients required in 1 year to optimize patient outcomes?
Limits: 2007-current; English
Filters: health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines

Database: Ovid MEDLINE(R) <1946 to October Week 3 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 30, 2012>, Embase <1980 to 2012 Week 43>
Search Strategy:

#	Searches	Results
1	exp Stroke/ or exp brain ischemia/	302769
2	exp intracranial hemorrhages/ use mesz	51645
3	exp brain hemorrhage/ use emez	74382
4	exp stroke patient/ use emez	6709
5	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab.	355108
6	or/1-5	557548
7	exp Hospital Units/ use mesz	71325
8	exp Stroke Unit/ use emez	1328
9	exp Skilled Nursing Facilities/ use mesz	3510
10	((stroke adj2 ward*) or (stroke adj2 unit*)).ti,ab.	5299
11	exp Patient Care Team/ use mesz	51084
12	Cooperative Behavior/ use mesz	24434
13	exp Nursing, Team/ use mesz	2063
14	exp "Delivery of Health Care, Integrated"/ use mesz	7547
15	exp interdisciplinary communication/	14834
16	exp TEAM NURSING/ use emez	28
17	exp Cooperation/ use emez	35084
18	exp TEAMWORK/ use emez	9751
19	exp Integrated Health Care System/ use emez	5797
20	((transitional or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin* or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat* or joint or multi-modal or multimodal) adj2 (care or	47190

	team*)).ti,ab.	
21	or/7-20	243134
22	6 and 21	8622
23	Meta Analysis.pt.	37145
24	Meta Analysis/ use emez	66797
25	Systematic Review/ use emez	54209
26	exp Technology Assessment, Biomedical/ use mesz	8878
27	Biomedical Technology Assessment/ use emez	11403
28	(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.	294827
29	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3796
30	exp Random Allocation/ use mesz	76252
31	exp Double-Blind Method/ use mesz	117819
32	exp Control Groups/ use mesz	1378
33	exp Placebos/ use mesz	31477
34	Randomized Controlled Trial/ use emez	331618
35	exp Randomization/ use emez	59833
36	exp Random Sample/ use emez	4276
37	Double Blind Procedure/ use emez	111601
38	exp Triple Blind Procedure/ use emez	35
39	exp Control Group/ use emez	38869
40	exp Placebo/ use emez	207241
41	(random* or RCT).ti,ab.	1390227
42	(placebo* or sham*).ti,ab.	449999
43	(control* adj2 clinical trial*).ti,ab.	38522
44	exp Practice Guideline/ use emez	279866
45	exp Professional Standard/ use emez	270060
46	exp Standard of Care/ use mesz	587
47	exp Guideline/ use mesz	23169
48	exp Guidelines as Topic/ use mesz	102637
49	(guideline* or guidance or consensus statement* or standard or standards).ti.	220073
50	(controlled clinical trial or meta analysis or randomized controlled trial).pt.	457414
51	or/23-50	2988431
52	22 and 51	2118
53	limit 52 to english language	1853
54	limit 53 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]	1515
55	limit 54 to yr="2007 -Current"	878
56	remove duplicates from 55	743
57	from 55 keep 1-878	878
58	from 56 keep 1-743	743

CINAHL

#	Query	Limiters/Expanders	Results
S26	S21 and S24	Limiters - Published Date from: 20070101-20121231; English Language; Age Groups: All Adult Search modes - Boolean/Phrase	114
S25	S21 and S24	Search modes - Boolean/Phrase	541
S24	S22 or S23	Search modes - Boolean/Phrase	339953
S23	((health technology N2 assess*) or meta analy* or metaanaly* or pooled analysis or (systematic* N2 review*) or published studies or medline or embase or data synthesis or data extraction or cochrane or random* or sham*or rct* or (control* N2 clinical trial*) or guideline* or guidance or consensus statement* or standard or standards or placebo*)	Search modes - Boolean/Phrase	334746
S22	(MH "Random Assignment") or (MH "Random Sample+") or (MH "Meta Analysis") or (MH "Systematic Review") or (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies") or (MH "Placebos") or (MH "Control (Research)") or (MH "Practice Guidelines") or (MH "Randomized Controlled Trials")	Search modes - Boolean/Phrase	124533
S21	S6 and S20	Search modes - Boolean/Phrase	1945
S20	(S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19)	Search modes - Boolean/Phrase	72020
S19	(MH "Nurse Liaison") OR "liaison"	Search modes - Boolean/Phrase	1904
S18	(MH "Collaboration")	Search modes - Boolean/Phrase	18201
S17	(MH "Interinstitutional Relations")	Search modes - Boolean/Phrase	5746
S16	(MH "Interprofessional Relations+")	Search modes - Boolean/Phrase	14551
S15	transitional N2 care or multidisciplin* N2 care or multifacet* N2 care or multi-disciplin* N2 care or multi-facet* N2 care or cooperat* N2 care or co-operat* N2 care or interdisciplin* N2 care or inter-disciplin* N2 care or collaborat* N2 care or multispecial* N2 care or multi-special* N2 care or share N2 care or sharing N2 care* or shared N2 care or integrat* N2 care or joint N2 care or multi-modal N2 care or multimedia N2 care or speciali* N2 care or dedicated N2 care	Search modes - Boolean/Phrase	31804
S14	transitional N2 team* or multidisciplin* N2 team* or multifacet* N2 team* or multi-disciplin* N2 team* or multi-facet* N2* team* or cooperat* N2 team* or co-operat* N2 team* or interdisciplin* N2 team* or inter-disciplin* N2 team* or collaborat* N2 team* or multispecial* N2 team* or multi-special* N2 team* or share N2 team* or sharing N2 team* or shared N2 team* or integrat* N2 team* or joint N2 team* or multi-modal N2 team* or multimedia N2 team* or speciali* N2 team* or dedicated N2 team*	Search modes - Boolean/Phrase	23711
S13	(MH "Health Care Delivery, Integrated")	Search modes - Boolean/Phrase	3683
S12	(MH "Team Nursing")	Search modes - Boolean/Phrase	321

S11	(MH "Cooperative Behavior")	Search modes - Boolean/Phrase	2559
S10	(MH "Multidisciplinary Care Team+")	Search modes - Boolean/Phrase	19363
S9	(stroke N2 ward*) or (stroke N2 unit*)	Search modes - Boolean/Phrase	1097
S8	(MH "Skilled Nursing Facilities")	Search modes - Boolean/Phrase	1778
S7	(MH "Stroke Units")	Search modes - Boolean/Phrase	222
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase	46226
S5	(MH "Stroke Patients")	Search modes - Boolean/Phrase	1991
S4	stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain N2 isch?emia or cerebral N2 isch?emia or intracranial N2 hemorrhag* or brain N2 hemorrhag*	Search modes - Boolean/Phrase	41485
S3	(MH "Intracranial Hemorrhage+")	Search modes - Boolean/Phrase	4989
S2	(MH "Cerebral Ischemia+")	Search modes - Boolean/Phrase	5857
S1	(MH "Stroke")	Search modes - Boolean/Phrase	26948

Cochrane Library

ID	SEARCH	HITS
#1	MeSH descriptor: [Stroke] explode all trees	4121
#2	MeSH descriptor: [Brain Ischemia] explode all trees	1967
#3	MeSH descriptor: [Intracranial Hemorrhages] explode all trees	1133
#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	16432
#5	#1 or #2 or #3 or #4	18151
#6	MeSH descriptor: [Hospital Units] explode all trees	2569
#7	MeSH descriptor: [Skilled Nursing Facilities] explode all trees	48
#8	((stroke near/2 ward*) or (stroke near/2 unit*)):ti and ((stroke near/2 ward*) or (stroke near/2 unit*)):ab	54
#9	MeSH descriptor: [Patient Care Team] explode all trees	1188
#10	MeSH descriptor: [Cooperative Behavior] explode all trees	504
#11	MeSH descriptor: [Nursing, Team] explode all trees	18
#12	MeSH descriptor: [Delivery of Health Care, Integrated] explode all trees	176
#13	MeSH descriptor: [Interdisciplinary Communication] explode all trees	89
#14	((transitional or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin* or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat* or joint or multi-modal or multimodal) near/2 (care or team*)):ti and ((transitional or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin* or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat* or joint or multi-modal or multimodal) near/2 (care or team*)):ab	200
#15	MeSH descriptor: [Interinstitutional Relations] explode all trees	41
#16	MeSH descriptor: [Interprofessional Relations] explode all trees	294
#17	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	4596
#18	#5 and #17 from 2007 to 2011	57

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	708
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES	189
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES	146
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))	2325
5	#1 OR #2 OR #3 OR #4	2430
6	MeSH DESCRIPTOR Hospital Units EXPLODE ALL TREES	477
7	MeSH DESCRIPTOR Skilled Nursing Facilities EXPLODE ALL TREES	9
8	(((stroke adj2 ward*) or (stroke adj2 unit*)))	66
9	MeSH DESCRIPTOR Patient Care Team EXPLODE ALL TREES	213
10	MeSH DESCRIPTOR Cooperative Behavior EXPLODE ALL TREES	41
11	MeSH DESCRIPTOR Nursing, Team EXPLODE ALL TREES	3
12	MeSH DESCRIPTOR Delivery of Health Care, Integrated EXPLODE ALL TREES	59
13	MeSH DESCRIPTOR interdisciplinary communication EXPLODE ALL TREES	18
14	MeSH DESCRIPTOR Interinstitutional Relations EXPLODE ALL TREES	5
15	MeSH DESCRIPTOR interprofessional relations EXPLODE ALL TREES	41
16	(((transitional or multidisciplin* or multifacet* or multi-disciplin* or multi-facet* or cooperat* or co-operat* or interdisciplin*or inter-disciplin* or collaborat* or multispecial* or multi-special* or share or sharing or shared or integrat* or joint or multi-modal or multimodal) adj2 (care or team*)))	616
17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1313
18	#5 AND #17	99
19	(#18) FROM 2007 TO 2012	38

Appendix 2: GRADE Tables

Table 1: GRADE Evidence Profile for Comparison of Patient Volume and Stroke Outcomes

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality							
2 (observational) (6;7)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Dose-response gradient (+1)[b]	⊕⊕ Low
Length of hospital stay							
1 (observational) (7)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Dose-response gradient (+1)[b]	⊕⊕ Low
Readmission							
1 (observational) (7)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	Dose-response gradient (+1)[b]	⊕⊕ Low

Abbreviation: No., number.
[a]Non-randomized design cannot preclude the presence of residual confounding or unmeasured confounders.
[b]Higher hospital volume was associated with fewer adverse outcomes across categories (6) and quartiles (6;7).

Table 2: Risk of Bias Among Observational Trials for the Comparison of Patient Volume and Stroke Outcomes

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Saposnik et al., 2007 (6)	No limitations	No limitations	No limitations	Limitations[a]	No limitations
Svendsen et al., 2012 (7)	No limitations	No limitations	No limitations	Limitations[b]	No limitations

[a]Administrative health data lacked information on factors for case-mix adjustment.
[b]Non-randomized design cannot exclude the presence of unmeasured or residual confounding.

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Transient Ischemic Attack: Where Can Patients Receive Optimal Care? 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.

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Permission Requests

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List of Abbreviations

ABCD^2	Age, Blood pressure, Clinical features, Duration, and Diabetes
CI	Confidence interval
CT	Computed tomography
ED	Emergency department
EXPRESS	Existing PREventive Strategies for Stroke
IQR	Interquartile range
MRI	Magnetic resonance imaging
PCP	Primary care physician
TIA	Transient ischemic attack

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.

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Objective of Analysis

Definitive strategies or guidelines supporting the necessity of hospital admission for patients with transient ischemic attack (TIA) do not currently exist. Since the majority of TIA patients do not experience an early stroke following an episode of TIA, it is unclear whether hospitalization is necessary for most TIA patients.

The objective of this rapid review is to investigate whether the place of initial assessment and treatment of patients who present with symptoms of TIA has an impact on the clinical outcomes.

Clinical Need and Target Population

Approximately 30% of strokes are preceded by TIA. (1) Early diagnosis and treatment is therefore critical to reduce mortality and disability in these patients.

The potential advantages of admission to hospital may include earlier administration of thrombolytic therapy in the event of stroke, early completion of diagnostic investigations, and higher rate of adherence to secondary prevention, for example, antihypertensive and lipid-lowering medications.

Definition

TIA was traditionally defined as any focal cerebral ischemic event in the brain or retina the symptoms of which last less than 24 hours. However, based on this definition, evaluation and treatment of TIA patients may not be initiated or completed by all health care professionals. In addition, even 2 neurologists may not agree on which events should be labelled as TIA.

More widespread use of imaging technologies has shown that about one-third of patients with TIA symptoms do in fact have cerebral infarction. This new information has led to the development of a new definition that incorporates imaging findings. This new definition of TIA is "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction." (2) Therefore, without diagnostic imaging it is not possible to make a distinction between TIA and stroke.

Risk of Stroke After TIA

In an international study of approximately 300,000 patients presenting to clinics and emergency departments (EDs) with TIA symptoms, the investigators classified 21% of the patients as high risk, 45% as moderate risk, and 34% as low risk. (3) Johnston et al (3) determined the risk of stroke during the first 90 days after TIA as follows:

- 3.9% within first 2 days
- 5.5% within 7 days
- 7.5% within 30 days
- 9.2% within 90 days

Various clinical prediction scores can help detect people at high risk of stroke. For example, $ABCD^2$ (Age, Blood pressure, Clinical features, Duration, and Diabetes) can classify people for urgent diagnosis and possible treatment. Figure 1 shows how to calculate $ABCD^2$ scores.

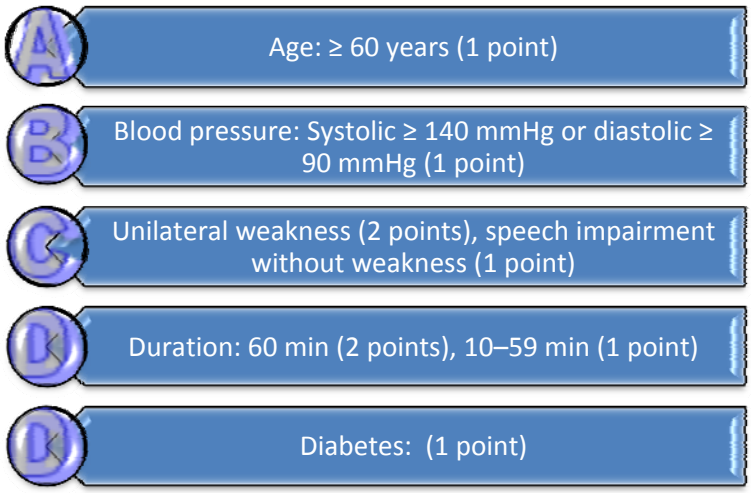

Figure 1: $ABCD^2$ Algorithm for Risk of Stroke Following Transient Ischemic Attack

More recently, imaging data have been included in the prediction scores ($ABCD^2$-I). The most recent version has added brain and vascular imaging to the risk algorithm to create a new prognostic score ($ABCD^3$ and $ABCD^3$-I). The combination of neuroimaging and vascular information has resulted in an improvement in the prognostic accuracy of the risk algorithm in patients with TIA.

Incidence of TIA and Stroke

In 1999–2000, 32,448 strokes led to a first stroke hospitalization in Canada. (4) The incidence of all types of stroke for hospitalized patients was 14.4 per 10,000 population in Canada. The incidence of hospitalized stroke was 15 times higher in those aged 80 years plus than those aged between 45 and 64 years (131.9 versus 8.7 per 10,000 population). The mean length of stay in hospital for all types of stroke was 21 days (95% confidence interval [CI], 20.0–21.4). Approximately 250,000 to 300,000 TIAs occur each year in the United States. (5)

In British Columbia, of the 8,548 first-ever stroke events in 2007–2008, about 60% were acute ischemic, 30% were TIA, and 10% were hemorrhagic events. (1) A survey in United States found that 1 in 15 people older than 65 years, equivalent to 2.3 million people, reported a history of TIA. (5)

Rapid Review

Research Question

Where should patients with signs and symptoms of transient ischemic attack (TIA) receive their initial care—including urgent assessment, appropriate diagnosis, and timely treatment—so as to maximize impact on the clinical outcomes?

Research Methods

Literature Search

A literature search was performed on September 28, 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 September 28, 2012.

Inclusion Criteria

- English language full-text reports
- publication between January 1, 2008, and September 28, 2012
- systematic reviews, meta-analyses, and health technology assessments

Exclusion Criteria

- non-English studies

Outcomes of Interest

- rate of stroke following TIA

Results of Literature Search

The database search yielded 85 citations published between January 1, 2008, and September 28, 2012 (with duplicates removed). The titles and abstracts of the retrieved articles were reviewed.

No systematic reviews comparing the benefit and safety of TIA initial care in hospital settings with those in outpatient settings were identified. Therefore, to provide the evidence for this rapid review based on clinical data as well as regulatory requirements, the literature was scanned for the most relevant observational studies published during the last 5 years. In addition, the National Guideline Clearinghouse and other information sources were searched for evidence-based guidelines on the early management of TIA or minor stroke.

Scanning of the literature identified 5 citations relevant to the study question. (6-10) A number of guidelines (listed below) were identified, and sections on the early management of TIA reviewed.

- The Canadian best practice recommendations for stroke care, published by the Canadian Stroke Network and last updated on December 2010, focuses on access and continuity of care (11)

- The Australian Clinical Guidelines for Stroke Management by the National Stroke Foundation, updated in 2010, include the guideline for stroke recognition and prehospital care and the guideline for early assessment and diagnosis (12;13)
- The United States National Stroke Association Guidelines for the Management of TIA, 2006 (14)
- The British Columbia guideline for stroke and TIA management and prevention developed by the Guidelines and Protocols Advisory Committee (GPAC), a joint committee of the British Columbia Medical Association and the British Columbia Ministry of Health, and published in 2009 (1)
- Guideline by the United Kingdom-based National Institute for Health and Clinical Excellence (NICE) on diagnosis and management of acute stroke and transient ischemic attack, published in 2008 (15)
- The Italian guidelines for stroke prevention, part of the Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration, published in 2000 (16)
- Scottish National Clinical Guideline on the management of patients with stroke or TIA by the Intercollegiate Guidelines Network (SIGN), published in 2008 (17)

Addressing the Research Question

To address the research question, different ways through which patients may first seek medical attention were considered. Patients may first seek medical attention through their primary care physicians (PCPs), medical emergency services, or EDs, or they may be referred directly to a hospital. Some organizations have developed rapid, outpatient TIA assessment clinics to expedite initial assessment and to facilitate early deployment of thrombolytic therapy if needed.

Primary Care Physician as the First Contact

No systematic reviews or guidelines were identified for initial evaluation of patients by a PCP. Goldstein et al (9) examined the outcomes of patients with first-ever TIA or stroke who were initially evaluated by their PCPs. The study included 95 patients with a first-ever TIA and 81 patients with stroke, based on medical record abstraction from 27 primary care medical practices in the eastern United States. Although stroke severity was not recorded, it was assumed that patients evaluated in the physicians' offices had minor deficits while those with more severe deficits were more likely referred to hospital EDs for initial evaluation. (9)

This study showed that establishing a clear distinction between TIA and minor stroke may be difficult if relying only on the patient's sign and symptoms. This may indicate the need for more objective diagnostic measures. The data from this study showed that there were no statistically significant differences in signs and symptoms between patients who had TIA and those who had stroke (Table 1). (9)

Table 1: TIA and Stroke Patients' Signs and Symptoms at Initial Contact with PCP

Sign or Symptom	TIA Patients (N = 95), %	Stroke Patients (N = 81), %	*P* Value
Limb weakness or numbness	46.3	50.6	0.57
Facial weakness	21.1	29.6	0.19
Speech disturbance			
Disarthria	15.8	21.0	0.37
Aphasia	12.6	11.1	0.76
Non-specified speech difficulty	5.3	3.7	0.61
Vision disturbance			
Visual loss	8.4	14.8	0.18
Visual blurring	7.4	6.2	0.75
Diplopia	7.4	6.2	0.75
Ataxia	16.8	23.5	0.27

Abbreviation: PCP, primary care physician; TIA, transient ischemic attack.
Source: Goldstein et al, 2000 (9)

Table 2 summarizes the events, tests ordered, and consultations with specialists at the initial evaluation of the stroke and TIA patients in the study. (9) Significantly more patients with stroke than with TIA were admitted to hospital or received brain imaging ($P = 0.04$); conversely, significantly more patients with TIA than with stroke received a carotid ultrasound ($P < 0.001$).

Table 2: Stroke and TIA Patients' Contact With Health Care Services

	TIA Patients (N = 95), %	Stroke Patients (N = 81), %	*P* Value
Event			
First contacted their PCP on the day their symptom occurred	80	88	0.12
Were admitted to a hospital for evaluation and treatment on the day of the index visit	2	10	0.03
Were not hospitalized and had no evaluations performed during the first month after presenting to a PCP	31	33	0.7
Tests ordered on the day of the initial contact			
Brain MRI/CT	23	37	0.04
Carotid ultrasound studies	40	14	< 0.001
ECG	18	21	0.6
Echocardiogram	19	14	0.34
MRA	2	0	0.2
Cerebral angiogram	1.1	2.5	0.47
Consultation			
Neurologists were consulted	14	20	-
Referred to a cardiologist	13	6	-
Vascular surgeons were consulted	6	3	-

Abbreviations: ECG, electrocardiogram; CT, computed tomography; MRA, magnetic resonance angiogram; MRI, magnetic resonance Imaging; PCP, primary care physician; TIA, transient ischemic attack.
Source: Goldstein et al, 2000. (9)

As shown in Table 2, only 23% of patients with TIA and 37% of patients with stroke received brain magnetic resonance imaging (MRI) or computed tomography (CT), indicating underuse of brain imaging.

Of the 176 patients in the study, 32% (31% with TIA and 33% with stroke) were not hospitalized and had no diagnostic studies performed during the first month after their first visit to PCP.

Medical Emergency Services as First Contact

Recommendations made by the Australian Clinical Guidelines for Stroke Management on stroke recognition and prehospital care (12) include the following:

- The general public should receive ongoing education on how to recognize the symptoms of stroke and the importance of early medical assistance (grade B).
- Ambulance services should assign high priority to stroke patients (grade C).
- Ambulance services should use a validated prehospital stroke **screening** tool and incorporate such tools into prehospital assessment of people with suspected stroke (grade B).
- Health and ambulance services should develop and use prenotification systems for stroke (grade C). (12)

Emergency Departments/TIA Clinics as the First Contact

The EXPRESS study (Existing PREventive Strategies for Stroke) (7) was a vigorous observational study of incident and recurrent TIA and stroke events in Oxfordshire, United Kingdom. It consisted of 2 phases. In phase 1 (April 1, 2002–Sept 30, 2004), all collaborating PCPs were asked to refer all patients with suspected TIA and minor stroke to a daily (weekdays only) hospital outpatient TIA and minor stroke clinic. The clinic then contacted the patient to arrange an appointment as soon as possible. The TIA clinic was appointment-based and as such had inherent delays in receiving referrals and contacting patients. Patients were seen at the clinic on weekdays or at home if the patient was too frail to attend the hospital. Brain imaging (usually CT) and an electrocardiogram (ECG) were conducted on the same day or shortly thereafter, and carotid ultrasound and transthoracic or transesophageal echocardiography (when clinically indicated) during the following week. Following assessment, a report consisting of the initial assessment and specific treatment recommendations was faxed to the PCP (usually within 24 hours). However, the clinic neither initiated any treatment nor issued any prescriptions; patients were only instructed to contact their PCPs as soon as possible. (7)

In phase 2 (October 1, 2004–March 31, 2007), the EXPRESS study team asked the collaborating PCPs to refer all patients suspected of having TIA or minor stroke directly to a clinic where no appointment was necessary (weekdays only) and at which the treatment was initiated immediately following a confirmed diagnosis. Patients were then assessed in the same way as in phase 1 but were given treatment on the same day if they were considered as having TIA or stroke. A report of assessment, diagnosis, and treatment protocol was faxed to the PCP as soon as possible (usually within 24 hours). Therefore, in phase 2, both the mode of access (no appointment necessary) and the time of initiation of treatment (immediately following a confirmed diagnosis) changed. (7)

Of the 620 patients with TIA or stroke who were referred to the hospital outpatient clinic, 591 (95%) were referred directly to the study clinics (310 in phase 1 and 281 in phase 2). Patients in phase 1 and phase 2 had generally similar baseline characteristics. In phase 1, the median time from seeking medical attention to first prescription of the medication recommended by the study clinic was 19 days (interquartile range [IQR], 6–48), whereas in phase 2 it was 1 day (IQR, 0–3; $P < 0.001$).

The results of the study showed that patients in phase 2 had significantly less 90-day rate of recurrent stroke (phase 1: 6 [2.1%], phase 2: 32 [10.3%]; adjusted hazard ratio [HR], 0.20, 95% confidence interval [CI], 0.08–0.49; $P = 0.0001$). In addition, the number of recurrent fatal strokes, the number of disabling strokes, and the overall number of fatal or disabling strokes were significantly less in phase 2 compared

with phase 1 (Table 3). The study concluded that urgent assessment and treatment of patients presenting with symptoms of TIA and minor stroke who nevertheless do not require immediate admission to hospital results in preventing about 80% of early recurrent stroke.

Table 3: Clinical Outcomes of Patients with TIA in Phase 1 and Phase 2 of the EXPRESS Study

Event	Phase 1 (N = 310), n (%)	Phase 2 (N = 281), n (%)	*P* Value
	90 days data		
Recurrent stroke	32 (10)	6 (2)	0.0001 HR, 0.20 (95% CI, 0.08–0.49)
Recurrent fatal stroke	8 (3)	1 (0.4)	0.027
Disabling stroke	8 (3)	0 (0)	0.007
Fatal or disabling stroke	16 (5)	1 (0.4)	0.0005
	6 months data		
Death at 6 months	14 (5)	9 (3)	0.41
Progression from no disability at baseline to disability	33 (11)	16 (6)	0.031
Died or became disabled	47 (15)	25 (9)	0.022 OR, 0.51 (95% CI, 0.30–0.85)

Abbreviations: CI, confidence interval; EXPRESS, Existing PREventive Strategies for Stroke; HR, hazard ratio; OR, odds ratio; TIA, transient ischemic attack.

Source: Luengo-Fernandez et al, 2009. (8)

In a separate publication, Luengo-Fernandez et al (8) reported the effect of the EXPRESS intervention on admission to hospital, costs, and disability (Table 4). The authors reported that urgent assessment and treatment of TIA or minor stroke reduced the overall number of days in hospital and generated savings of £624 (GBP) per each patient referred to the TIA clinic. In phase 2, the clinic cost was not included in the analysis. When the data was extrapolated to the population of 1 million individuals, it was equal to the prevention of about 165 strokes annually and a saving of 4,790 hospital bed-days, with monetary saving of £1.12 million (GBP).

Most patients (n = 484 [82%]) were not admitted to the hospital, and therefore did not incur any hospital-related costs.

Table 4: Comparison of EXPRESS Phase 1 and 2 for Hospitalization, Length of Stay, and Costs

Event	Phase 1 (N = 310)	Phase 2 (N = 281)	*P* Value
All cause admission to hospital, n (%)	57 (18)	50 (18)	0.85
Days in hospital due to vascular causes	1,365	427	0.016
Days in hospital due to recurrent stroke	1,147	90	0.005
Days in hospital due to other vascular disease	218	337	0.31
Cost, £ (GBP)			
Total cost	327,474	121,506	-
Mean (SD) cost	1,056 (4,879)	432 (2,277)	0.03
Mean (SD) cost for recurrent stroke	866 (4,788)	76 (998)	0.003
Mean (SD) cost for other vascular cause	191 (1,102)	356 (2,508)	0.19

Abbreviation: EXPRESS, Existing PREventive Strategies for Stroke; SD, standard deviation.

Source: Luengo-Fernandez et al, 2009. (8)

Olivot et al (10) evaluated consecutive patients at a novel ED-based TIA triage system in Stanford, United States, for suspicious TIA. Of the 224 patients in the study, 206 (92%) were seen within 24 hours of symptom onset. At initial evaluation, 157 patients (70%) were discharged to a TIA clinic and 67 (30%) were hospitalized. The median time from symptom onset to ED visit was 3 days, and the median time from ED visit to TIA clinic was 4 days. Of the 157 patients discharged to the TIA clinic, 51 (32%) had a

final diagnosis of a cerebrovascular event (46 TIA and 5 minor stroke), and an additional 19 (6%) had a final diagnosis of "possible TIA." (10)

The rate of vascular outcome events for the 157 patients who were referred to the TIA clinic was 0.6% (IQR, 0.1–3.5) at 7 days, and there were no additional outcome events between 7 and 90 days. (10) The stroke rate in patients who were hospitalized was 1.5% (0.3%–8.0%). (10) The combined group had a stroke rate of 0.9% (0.3%–3.2%), which was significantly less than the expected rate at 7 days (4.0%; $P = 0.034$) and 90 days (7.1%; $P = 0.001$) based on $ABCD^2$ (Age, Blood pressure, Clinical features, Duration, and Diabetes) scores. (10)

The SOS-TIA study (6) evaluated the effect of rapid assessment of patients with TIA on clinical decision making, length of hospital stay, and rate of stroke. The SOS-TIA was a hospital-based TIA clinic in France with 24/7-access that was organized to provide an initial standardized assessment of patients within 4 hours of admission. The SOS-TIA clinic, located in the neurology department of a University hospital with a stroke unit, mailed a leaflet on TIA to 15,000 family doctors, cardiologists, neurologists, and ophthalmologists in Paris and its administrative region and to the EDs of community and teaching hospitals. The leaflet contained all the necessary information about TIA and also informed doctors of the availability of the clinic. Apart from being open 24 hours, 7 days a week, the TIA clinic could also be contacted via a toll-free telephone number.

Between January 2003 and December 2005, 1,085 patients with suspected TIA entered the SOS-TIA program. Clinical assessments were performed by vascular neurologists and, if TIA was suspected, further comprehensive tests were initiated. The vascular neurologist was responsible for deciding whether to exclude patients who were judged to have nonischemic transient symptoms such as migraine. After completion of the evaluation, the vascular neurologist contacted the referral doctor to discuss the diagnosis and the most appropriate treatment for patient. Patients were discharged home immediately after the assessment, unless they fulfilled predefined criteria for admission to the hospital stroke unit. If patients needed antithrombotic therapy (for minor stroke, TIA, and possible TIA), it was started immediately. The family doctors received their patients' discharge summaries including the targets of the prevention therapy. Whether family doctors followed recommendations made by the TIA clinic was not recorded.

A mean of 30 patients were seen at the SOS-TIA clinic each month, and a neurologist saw 946 patients (87%) within 24 hours of initial contact. Baseline characteristics of patients with minor stroke, definite TIA, possible TIA, and those with nonischemic diagnosis were similar.

Of the 946 patients seen by a neurologist, 227 (21%) were admitted to the stroke unit for a mean length of stay of 4 days (IQR, 2–7). The remaining 808 (74%) were judged not to need hospital admission and were discharged home after completion of the examinations. Of these, 478 had a definite TIA or a minor stroke. After their visit to the SOS-TIA clinic, 1,052 (97%) patients were followed up for a median of 16 months (IQR, 12–19); 33 were lost to follow-up.

All the incidents of stroke occurred in patients with definite TIA except 1 that occurred in a patient diagnosed with possible TIA. Patients with the diagnosis of definite TIA and a recent ischemic brain lesion had the highest risk of stroke (Table 5).

Table 5: Observed and Expected Rate of Stroke at 90 Days in Patients Evaluated in a Hospital-Based TIA Clinic

Patients	Observed Rate of Stroke at 90 Days by Kaplan-Meier Analysis, % (95% CI)	Expected Rate of Stroke at 90 Days Based on ABCD^2, %
All patients (N = 1,052)	1.24 (0.72–2.12)	5.96
TIA without new lesion (n = 524)	1.34 (0.64–2.78)	6.13
TIA with new lesion (n = 105)	4.76 (2.01–11.06)	7.76
Possible TIA (n = 141)	0.71 (0.10–4.93)	4.00

Abbreviations: ABCD^2, Age, Blood pressure, Clinical features, Duration, and Diabetes; CI, confidence interval; TIA, transient ischemic attack.
Source: Lavallee et al, 2007. (6)

One year outcomes are shown in Table 6. However, there was no historical control to compare the results at 1 year.

Table 6: Rate of Stroke and Combined Outcomes at 1 Year in Patients Evaluated in a Hospital-Based TIA Clinic

Patients	All Stroke, % (95% CI)	All Stroke, MI, and Vascular Death, % (95% CI)
All patients (N = 1,052)	1.95 (1.26–3.00)	2.54 (1.74–3.72)
TIA without new lesion (n = 524)	2.17 (3.89–1.20)	2.78 (1.65–4.65)
TIA with new lesion (n = 105)	4.76 (2.01–11.06)	5.74 (2.62–12.34)
Minor stroke (n = 54)	1.96 (0.28–13.12)	3.81 (0.97–14.39)
Possible TIA (n = 141)	2.18 (0.71–6.66)	2.18 (0.71–6.66)
Other diagnosis (n = 228)	No events	0.48 (0.07–3.36)

Abbreviation: MI, myocardial infarction; TIA, transient ischemic attack.
Source: Lavallee et al, 2007. (6)

Recommendations from Guidelines

Recommendations developed by British Columbia Guidelines and Protocols Advisory Committee (1) include the following:

- Consider stroke and emergent TIAs as medical emergencies and perform investigations and treatment as soon as possible. Immediately send patients suspected of having an acute stroke to an ED by ambulance; most will be admitted to hospital for initial care and treatment.
- Consider patients with an emergent TIA for admission.
- The initial investigations for emergent TIAs and suspected acute stroke are the same.
- Patients diagnosed with a nonemergent TIA may be referred to an internist/neurologist or (if available) to a rapid stroke assessment unit. Alternately, a physician may decide to investigate/manage patients diagnosed with a nonemergent TIA as outpatients. (1)

The Canadian Stroke Network (11) best practice recommendations on acute stroke management include the following:

- Patients admitted to hospital because of an acute stroke or TIA should be treated in an interprofessional stroke unit (Evidence level A).
- Patients should be admitted to a stroke unit that is a specialized, geographically defined hospital unit dedicated to the management of stroke patients (Evidence level A).
- The core interprofessional team in the stroke unit should consist of health care professionals with stroke expertise in medicine, nursing, occupational therapy, physiotherapy, speech–language pathology, social work, and dietetics (Evidence level A).
- The interprofessional team should assess patients within 48 hours of admission and formulate a management plan (Evidence level C).
- Clinicians should use standardized, valid assessment tools to evaluate patients' stroke-related impairments and functional status (Evidence level B). (11)

The Australian Clinical Guidelines for Stroke Management recommend the following for early assessment and diagnosis and rapid assessment in the ED: (13)

- Initial diagnosis should be reviewed by a clinician expert in the evaluation of stroke (Grade C).
- Stroke severity should be assessed and recorded on admission by a trained clinician using a validated tool (Grade C).
- ED staff should use a validated stroke screening tool to assist in rapid accurate assessment for all people with stroke (Grade C).
- All patients with suspected stroke should have an urgent brain MRI/CT immediately where facilities are available (within 24 hours) (grade A).
- A repeat MRI/CT and acute medical review should be considered urgently when a patient's condition deteriorates (grade good practice point).
- All patients with carotid territory syndromes who could potentially be candidates for carotid revascularization should have urgent carotid imaging (grade B).
- Further brain, cardiac, or carotid imaging should be undertaken in select patients (grade B). (13)

Clinical tests recommended by the Australian Clinical Guidelines for Stroke Management for early assessment and diagnosis of patients with TIA admitted to an ED are listed in Table 7.

Table 7: Recommendations for Early Assessment and Diagnosis of Patients with TIA

Patient	Detailed History	Prognostic Scores	Blood Tests	Brain Imaging	Carotid Imaging	Grade
All patients with suspected TIA (defined as those whose symptoms and signs have completely resolved within 24 hours) whether first seen in primary or secondary care				Patients with suspected TIA should be assessed by a specialist within 1 week of symptom onset before making a decision for brain imaging		B
Patients identified as high risk, e.g., $ABCD^2$ score ≥ 4 and/or any of the following: AF, carotid territory symptoms, crescendo TIA				Urgent or immediately where available (within first 24 hours); preferably MRI with diffusion-weighted imaging	Urgently in those patients with anterior circulation symptoms who are candidates for carotid revascularization	B
Patients classified as low risk, e.g., $ABCD^2$ scores < 4 without AF or carotid territory symptoms, or patients who presented more than 1 week after last symptoms				As soon as possible (within 48 hours)	Where indicated and as soon as possible (within 48 hours)	B

Abbreviations: $ABCD^2$, Age, Blood pressure, Clinical features, Duration, and Diabetes; AF, atrial fibrillation; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

Source: National Stroke Foundation, 2010. (13)

The Italian guidelines for stroke prevention, part of the Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration, (16) include the following recommendation:

> For patients presenting with TIA, prompt hospital admission is recommended when symptoms are recurrent and last more than 1 hour, and when there is a possible embolic source (arterial or cardiac) (Grade A). (16)

The Guidelines developed by National Institute for Health and Clinical Excellence (NICE) on diagnosis and management of acute stroke and transient ischemic attack (15) include the following:

- People who are admitted to an ED with suspected stroke or TIA should have the diagnosis established rapidly using a validated tool such as ROSIER (Recognition of Stroke in Emergency Room).
- People who have had a suspected TIA should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system such as $ABCD^2$.
- People who have had a suspected TIA and who are at high risk of stroke ($ABCD^2$ score ≥ 4) should be assessed by a specialist for appropriate investigation and treatment within 24 hours of onset of symptoms.
- People with crescendo TIA (2 or more TIAs in a week) should be treated as being at high risk of stroke, even though they may have an $ABCD^2$ score of ≤ 3. (15)

The Scottish National Clinical Guideline by the Intercollegiate Guidelines Network (17) includes the following:

- Emergency medical services should be redesigned to facilitate rapid access to specialist stroke services.
- Patients with TIA and minor stroke, who are at high risk of early recurrence, should undergo specialist assessment and begin treatment promptly.
- Stroke patients requiring admission to hospital should be admitted to a stroke unit staffed by a coordinated multidisciplinary team with a special interest in stroke care.
- In areas where there is no stroke unit, telemedicine consultation with a hospital with a stroke specialist or other appropriate resources should be considered as soon as possible to facilitate treatment in patients eligible for thrombolysis.

Conclusions

It is of utmost importance that assessment and treatment be initiated as soon as possible when patients present with symptoms of transient ischemic attack (TIA) or minor stroke. This can be done either through referral to a TIA clinic or an emergency department (ED) with stroke expertise and suitable diagnostic facilities.

Evidence from trials of treatment of acute TIA or minor stroke suggests that the relative benefit of interventions is greater in the acute phase. The EXPRESS study demonstrated that urgent assessment and early treatment of TIA or minor stroke reduced the risk of early recurrent stroke by about 80%. (7) Disability, days in hospital, and hospital costs as a result of recurrent stroke were significantly reduced. (8) Most patients (82%) were not admitted to the hospital following appropriate assessment in a TIA clinic where a senior neurologist reviewed all the cases and classified them as TIA, stroke, or other conditions. (8)

Several evidence-based guidelines have made recommendations for urgent assessment, diagnosis, and treatment of patients with TIA. The following points are the key recommendations from these guidelines:

- TIA should be considered as an urgent and time-dependent condition.
- Rapid and complete diagnostic evaluation and timely initiation of treatment in TIA patients are the key points to preventing a major stroke.
- The initial investigations for emergent TIAs and suspected acute stroke are the same.
- All TIA patients should be evaluated by health care professionals with stroke expertise and in facilities where appropriate diagnostic tests can be performed and where treatment can be initiated within 24 hours.
- TIA clinics should have personnel with expertise in TIA diagnosis and management.
- For patients in rural settings or with inadequate critical resources, telemedicine linkage with a hospital with appropriate resources should be considered as soon as possible.
- Patients suspected of having a stroke or having an emergent TIA should be admitted to a stroke unit dedicated to the management of stroke patients.
- Risk stratification using validated scoring systems should be used in clinical practice to identify patients at high or low risk of stroke. Patients can then receive appropriate diagnostic tests according to their risk score.
- The general public should receive ongoing education on how to recognize the symptoms of TIA or stroke and the importance of early medical assistance.

In conclusion, provision of clinical services with stroke expertise, adequate imaging, and laboratory facilities for urgent assessment and timely treatment of patients with TIA and minor stroke is effective in reducing the incidence of subsequent stroke and its associated costs.

Acknowledgements

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Appendix

Final Literature Search – Stroke Mega-Analysis Rapid Review – TIA Clinics

Search date: September 28, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD

Q: Urgent treatment for transient ischaemic attack/TIA clinics and other service delivery models for TIA management
Limits: 2008-current; English (Human & Adult limits not recommended for MA/SR/HTA)
Filters: health technology assessments, systematic reviews, and meta-analyses

Database: Ovid MEDLINE(R) <1946 to September Week 3 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 27, 2012>, Embase <1980 to 2012 Week 38>
Search Strategy:

#	Searches	Results
1	Ischemic Attack, Transient/ use mesz	16920
2	Transient Ischemic Attack/ use emez	21346
3	(transient ischemic attack? or transient ischaemic attack? or transient ischemic seizure? or circulatory epilepsy or transient brain ischemia? or TIA? or (ischemia? adj (transient cerebral or transient brainstem or transient brain stem))).ti,ab.	27890
4	((cerebral ischemia? or ischemic attack?) adj transient).ti,ab.	71
5	or/1-4	52382
6	Ambulatory Care Facilities/ use mesz	11014
7	Ambulatory Care/ use mesz	33992
8	Monitoring, Ambulatory/ use mesz	4671
9	Outpatient Clinics, Hospital/ use mesz	13868
10	Secondary Prevention/	13582
11	Outpatient Department/ use emez	34777
12	exp Ambulatory Care/ use emez	35644
13	(ambulatory* or care center* or care centre* or clinic? or clinic-based).ti,ab.	601034
14	or/6-13	681038
15	((transient ischemic attack? or transient ischaemic attack? or transient ischemic seizure? or circulatory epilepsy or transient brain ischemia? or TIA?) adj5 (ambulatory* or care center* or care centre* or (care* adj3 model*) or clinic? or clinic-based or inpatient* or in-patient* or management* or outpatient* or out-patient* or rapid-access* or specialist? or specialist-clinic? or specialist-service? or urgent care* or urgent-assessment* or urgent-access*)).ti,ab.	2867
16	Meta Analysis.pt.	36479
17	Meta Analysis/ use emez	65909
18	Systematic Review/ use emez	53173
19	exp Technology Assessment, Biomedical/ use mesz	8853
20	Biomedical Technology Assessment/ use emez	11380
21	(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.	289866

22	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3640
23	or/16-22	349549
24	((5 and 14) or 15) and 23	281
25	limit 24 to english language	258
26	limit 25 to yr="2008 -Current"	119
27	remove duplicates from 26	89

Cochrane Library

Line #	Terms	Results
#1	MeSH descriptor: [Ischemic Attack, Transient] this term only	472
#2	transient ischemic attack? or transient ischaemic attack? or transient ischemic seizure? or circulatory epilepsy or transient brain ischemia? or TIA? or (ischemia? next (transient cerebral or transient brainstem or transient brain stem)):ti,ab,kw or (cerebral ischemia? or ischemic attack?) next transient:ti,ab,kw (Word variations have been searched)	303
#3	#1 or #2	676
#4	MeSH descriptor: [Ambulatory Care Facilities] this term only	319
#5	MeSH descriptor: [Ambulatory Care] this term only	2773
#6	MeSH descriptor: [Monitoring, Ambulatory] this term only	348
#7	MeSH descriptor: [Outpatient Clinics, Hospital] this term only	524
#8	MeSH descriptor: [Secondary Prevention] this term only	115
#9	ambulatory* or care center* or care centre* or clinic? or clinic-based:ti,ab,kw (Word variations have been searched)	23172
#10	#4 or #5 or #6 or #7 or #8 or #9	23274
#11	(transient ischemic attack? or transient ischaemic attack? or transient ischemic seizure? or circulatory epilepsy or transient brain ischemia? or TIA?) near/5 (ambulatory* or care center* or care centre* or (care* near/3 model*) or clinic? or clinic-based or inpatient* or in-patient* or management* or outpatient* or out-patient* or rapid-access* or specialist? or specialist-clinic? or specialist-service? or urgent care* or urgent-assessment* or urgent-access*):ti,ab,kw (Word variations have been searched)	29
#12	(#3 and #10) or #11	19 from 2008 to 2012

CDSR=1
DARE=1
HTA=1

CRD

Search	Hits	
1	MeSH DESCRIPTOR Ischemic Attack, Transient IN DARE,HTA	27
2	(transient ischemic attack? OR transient ischaemic attack? OR transient ischemic seizure? OR circulatory epilepsy OR transient brain ischemia? OR TIA? OR (ischemia? ADJ (transient cerebral OR transient brainstem OR transient brain stem))):TI OR ((cerebral ischemia? OR ischemic attack?) ADJ transient):TI IN DARE, HTA	17
3	#1 OR #2	36
4	MeSH DESCRIPTOR Ambulatory Care Facilities IN DARE,HTA	29
5	MeSH DESCRIPTOR Ambulatory Care IN DARE,HTA	110

6	MeSH DESCRIPTOR Monitoring, Ambulatory IN DARE,HTA	39
7	MeSH DESCRIPTOR Outpatient Clinics, Hospital IN DARE,HTA	15
8	MeSH DESCRIPTOR Secondary Prevention EXPLODE ALL TREES	35
9	(ambulatory* OR care center* OR care centre* OR clinic? OR clinic-based):TI IN DARE, HTA	91
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	272
11	#3 AND #10	1
12	((transient ischemic attack? OR transient ischaemic attack? OR transient ischemic seizure? OR circulatory epilepsy OR transient brain ischemia? OR TIA?) ADJ5 (ambulatory* OR care center* OR care centre* OR (care* ADJ3 model*) OR clinic? OR clinic-based OR inpatient* OR in-patient* OR management* OR outpatient* OR out-patient* OR rapid-access* OR specialist? OR specialist-clinic? OR specialist-service? OR urgent care* OR urgent-	0

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Optimal Onset-to-Admission Interval for Inpatient Stroke Rehabilitation: A Rapid Review (Pre-Edit)

Health Quality Ontario

January 2013

Suggested Citation

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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.

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Table of Contents

List of Abbreviations

BI	Barthel Index
FIM	Functional Independence Measure
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IQR	Inter Quartile Range
OAI	Onset-to-admission interval
TIA	Transient ischemic attack

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.

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Objective of Analysis

The objective of this rapid review is to determine the optimal onset-to-admission interval (OAI) for inpatient stroke rehabilitation therapy.

Clinical Need and Target Population

Description of Disease/Condition

A stroke is a sudden loss of brain function caused by the interruption of blood flow to the brain (ischemic stroke) or the rupture of blood vessels in the brain (hemorrhagic stroke). A stroke can affect any number of functions, including the ability to move, see, remember, speak, reason, read, or write. (1) Approximately 80% of strokes are ischemic and 20% are hemorrhagic. (1) A transient ischemic attack (TIA), also known as a "mini-stroke," is caused by a temporary interruption of blood flow to the brain. A TIA is an important warning sign that individuals are at increased risk of stroke. (1)

Prevalence and Incidence

Stroke is the leading cause of adult neurological disability in Canada, with 300,000 people or 1% of the population, living with its effects. (2)

Ontario Prevalence and Incidence

In 2009, 10,238 males and 9,764 females presented to an emergency department in Ontario with a stroke or a TIA. (3) The mean age was 72.3 years and over half were 66–84 years of age. Thirty-seven per cent were people with a TIA, 4.9% with an ischemic stroke, and 8.5% hemorrhagic; the stroke type was not specified as ischemic or hemorrhagic on the health records of the remainder (50%). (3) Only about 1 in 3 stroke/TIA patients seeks medical attention within 2.5 hours of stroke onset. (3)

Ontario Context

Approximately 20,000 people experience a stroke annually in Ontario. Of these, 3,000 are admitted to inpatient rehabilitation. (4) Of all acute stroke inpatients, 21% receive inpatient rehabilitation. The median number of days from the onset of stroke to admission to inpatient rehabilitation was 11 days in 2009/10 with a regional variation in wait times for rehabilitation admission of 6 days. (3) Of people eligible for

inpatient stroke rehabilitation in Ontario, 19% remained in an acute care facility longer than needed while waiting for access to a rehabilitation bed in an inpatient facility. (5)

Technology/Technique

Of the two-thirds of people who survive an initial stroke episode, nearly half are left with sensorimotor, perceptual, cognitive, and/or musculoskeletal deficits. (6) Post-stroke rehabilitation interventions have been used to increase functional status and quality of life in the weeks after a stroke. (6) Once medically stable, people who have experienced stroke may receive rehabilitation therapy in an inpatient stroke rehabilitation program. People who receive care in an organized rehabilitation stroke unit have reduced rates of mortality, institutionalization, and dependency. The OAI is defined as being the number of days that elapse between the onset of stroke and admission to an inpatient stroke rehabilitation program. The OAI ought to be as short as possible to maximize functional outcomes after stroke. Practice standards for inpatient stroke rehabilitation suggest that the wait time from when the stroke survivor is referred to rehabilitation services until the start of all appropriate rehabilitation services be no more than 2 days. (7)

Rapid Review

Research Question

What is the optimal onset-to-admission interval (OAI) time for inpatient stroke rehabilitation therapy?

Research Methods

Literature Search

A literature search was performed between May 17, 2012, and May 22, 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, 2000, until May 22, 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-text reports
- published between January 1, 2000, and May 22, 2012
- randomized controlled trials (RCTs), systematic reviews with or without a meta-analyses, and observational studies
- studies that evaluate the timing of stroke rehabilitation
- adult (> 18 years of age) stroke population
- ischemic and hemorrhagic stroke
- reports on one of the following outcomes including Barthel Index (BI), death, or a measure of dependency.

Exclusion Criteria

- studies that compare intervention to control in the early stroke rehabilitation period

Outcomes of Interest

- death
- dependency or function (defined as institutionalization or using a BI score or modified Rankin Score or total Functional Independence Measure [FIM] score.)

Expert Panel

In February 2012, an Expert Advisory Panel on Stroke Management was struck. Members of the panel included physician experts in stroke care, members of the Ontario Stroke Network, and Ontario Local Health Integrated Networks.

The role of the Expert Advisory Panel on Stroke Management was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate interventions for the management of stroke in the Ontario health care setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the Stroke Expert Advisory Panel members.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (8) The overall quality was determined to be very low, low, moderate, or high using a stepwise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs 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. (8) For more detailed information, please refer to the latest series of GRADE articles. (8)

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 4,992 citations published between January 1, 2000, and May 22, 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.

Two systematic reviews met the inclusion criteria. From these, 1 RCT and 7 observational studies were included and form the body of evidence for this rapid review.

For each included study, the study design was identified and is summarized below in Table 1, which is a modified version of a hierarchy of study design by Goodman. (9)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs/meta-analysis	2
Large RCT	
Small RCT	1
Observational Studies	**7**
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	10

Abbreviation: RCT, randomized controlled trial.

Results

The literature search found 2 systematic reviews. (10;11) Neither review used GRADE Working Group criteria to evaluate the body of evidence.

Very Early Mobilization

A systematic review by Bernhardt et al (10) for the Cochrane Collaboration determined whether very early mobilization (VEM) in the acute stroke patient improves recovery compared with usual care. The Assessment of Multiple Systematic Reviews (AMSTAR) score for this review was 10. (12) The review's systematic search of multiple databases yielded 39 trials of which 1 randomized controlled trial (RCT), A Very Early Rehabilitation Trial (AVERT II), met the a priori inclusion criteria for this rapid review. The characteristics of the study population and RCT are shown in Table A1 of Appendix 2. In the AVERT II trial (completed in Australia), people were randomized to receive first mobilization within 24 hours of stroke by a nurse and a physiotherapist. Those in the control group received mobilization 48 hours post stroke as per usual care. The primary outcome measure of the systematic review was the number of people that died or where dependent (poor outcome) at 3 months after the stroke. Poor outcome was defined as modified Rankin Score of 3 to 6. Seventy-one people were enrolled in the RCT with 75% having mild to moderate stroke as measured by the National Institute of Stroke Health Scale score (mild stroke: 1–7, moderate stroke 8–16). The median time to first mobilization after symptom onset was 18.1 hours (interquartile range [IQR]: 12.8–21.5) in the early mobilization group and 30.8 hours (IQR: 23.0–39.9) in the usual care group ($P < 0.001$). Data from the 71 participants indicated that there was a nonsignificant increase in death (8/38, 21.1% vs. 3/33, 9.1%) (Figure 1) and a nonsignificant decrease in dependency (23/38, 60.5% vs. 23/33, 69.7%) (Figure 2) in the VEM group compared with the controls at 3 months. There was a nonsignificant difference in dependency and death at 6 and 12 months between the VEM group and the usual care group. The authors of the systematic review concluded that there is insufficient evidence regarding the benefits or harm of VEM after stroke to make any recommendation on the practice. (10) The review acknowledged that this evidence does not suggest that the practice of VEM ought to be discontinued in countries where it is a standard practice; rather, they considered that there is insufficient evidence to suggest the practice ought to be adopted more widely. (10) The body of evidence for both of these outcomes comprises 1 RCT. The risk of bias assessment for this RCT is shown in Appendix 3. The GRADE level for the body of evidence for each outcome is low (Appendix 4).

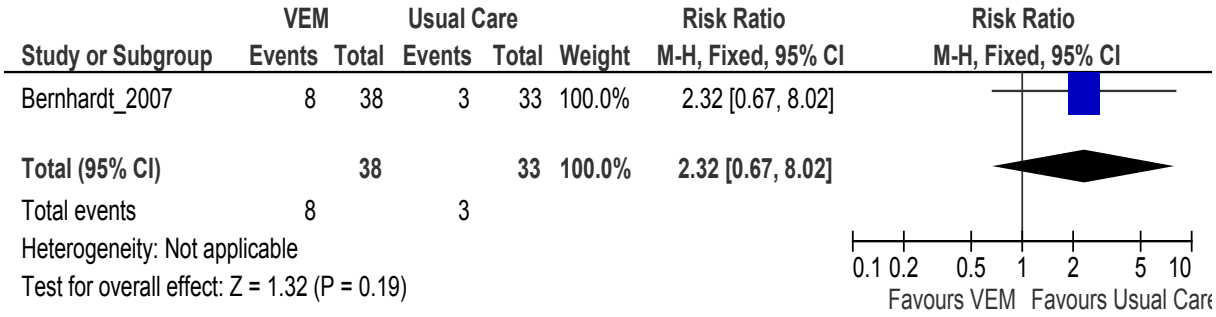

Figure 1: Forest Plot of Death at 3 Months Post Stroke

Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; VEM, very early mobilization.

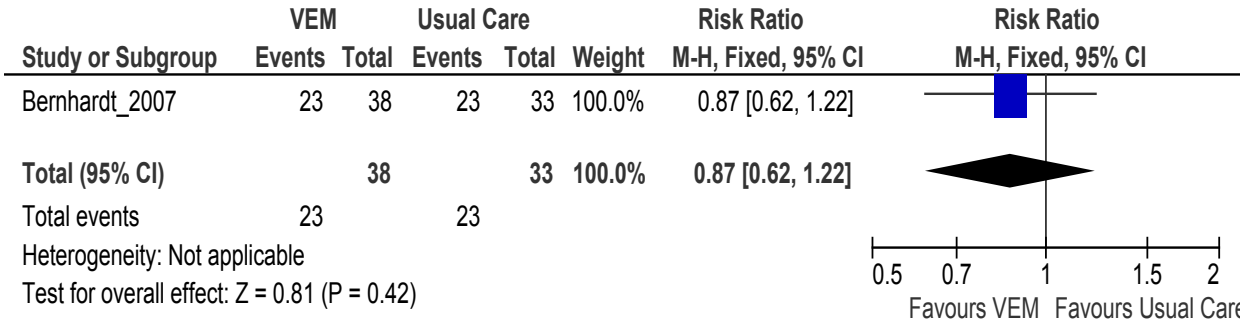

Figure 2: Forest Plot of Dependency at 3 Months Post Stroke

Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; VEM, very early mobilization.

Stroke Rehabilitation Evidence-Based Review

The Stroke Rehabilitation Evidence-Based Review (SREBR), updated in 2011, determined the optimal timing to begin inpatient stroke rehabilitation. (11) The AMSTAR score for this review was 10. (12) The review's systematic search of multiple databases yielded 7 relevant observational studies. The characteristics of these 7 observational studies are described in Appendix 2 (Table A1). The mean age of the population in these 7 studies ranged from 60 to 71 years. The proportion of stroke type in each study population is reported in Table 2.

Table 2: Proportion of Stroke Types Included in SREBR Observational Studies

Type of Stroke	Hu et al, 2010 (13)	Huang et al, 2009 (14)	Salter et al, 2006 (15)	Gagnon et al, 2006 (16)	Maulden et al, 2005 (17)	Musicco et al, 2003 (18)	Paolucci et al, 2000 (19)
Ischemic, %	60	66	86	NR	75	NR	84
Hemorrhagic, %	40	34	14	NR	25	NR	16
Mild, %	11	NR	NR	NR	0	0	NR
Moderate, %	44	NR	NR	NR	50	NR	NR
Severe, %	45	NR	NR	NR	50	NR	NR

Abbreviations: NR, not reported; SREBR, Stroke Rehabilitation Evidence-Based Review..

The results of each study for the outcomes death and dependency are reported in Table 3.

Table 3: Proportion of Stroke Types Included in SREBR Observational Studies

Study	Design	Analysis	Outcome
Hu et al, 2010 (13)	Prospective Cohort	Regression	In a multiple linear regression model for predictors of BI at discharge from inpatient rehabilitation, time to start of rehabilitation (OAI) was a significant predictor. Starting rehabilitation 1 day earlier resulted in a 0.65 point increase in the BI score at discharge ($P = 0.02$). People who start rehabilitation earlier had a higher BI score at discharge. OAI was significantly correlated with BI score at discharge after controlling for initial severity and age.
Huang et al, 2009 (14)	Retrospective Cohort	Regression	In a stepwise multivariate linear regression for predictors of BI at various time points post stroke, time to start of rehabilitation was a significant predictor of BI at 3 months, 6 months and 1 year. Starting rehabilitation 1 day earlier resulted in a 2.45 point increase in the BI score at 3 months ($P < 0.01$), a 2.49 increase at 6 months ($P < 0.01$), and a 4.98 increase in BI score at 1 year ($P < 0.01$). Starting rehabilitation 1 day earlier also resulted in a 2.44 improvement in BI score at 3 months ($P < 0.01$), a 1.87 improvement at 6 months ($P < 0.00$), and a 5.05 improvement at 1 year ($P < 0.01$).
Salter et al, 2006 (15)	Retrospective Cohort	Multivariate analysis of variance	Statistically significant differences in age-adjusted discharge FIM scores between people admitted 0–15 days and 16–30 days post stroke. Those admitted earlier had higher discharge FIM scores compared with those admitted later (106 vs. 95 respectively, $P < 0.01$). The OAI was inversely associated with discharge FIM score ($r = -0.432$, $P < 0.01$). The shorter the OAI the higher the discharge (greater independence) FIM score.
Gagnon et al, 2006 (16)	Retrospective Cohort	Analysis of variance	120 participants were matched on 3 variables, degree of stroke severity, gender, and age, and equally distributed into 3 OAI subgroups, short (< 20 days), moderate (20–40 days) and long (> 40 days; ≤ 70 days). The total FIM score was not significantly different among the 3 OAI groups ($P = 0.083$). The authors concluded that, where rehabilitation services are rapidly initiated in acute care settings after stroke, the OAI may not be a relevant prognostic factor of inpatient stroke rehabilitation outcomes.
Maulden et al, 2005 (17)	Prospective Cohort		In a multiple linear regression model for predictors of total FIM score at discharge from inpatient rehabilitation, OAI for rehabilitation was a significant predictor. Rehabilitation started 1 day earlier in people with moderate stroke severity resulted in a 0.11 point increase in the total FIM score at discharge ($P = 0.004$). For those with severe stroke, starting rehabilitation 1 day earlier resulted in a 0.15 point increase in the total FIM score at discharge.
Musicco et al, 2003 (18)	Prospective Cohort study		There was no significant difference in the probability of death relative to the OAI interval. Compared to people with an OAI of ≤ 7 days, those with an OAI of 8–14 days had a nonsignificant 10% lesser chance of death post stroke and those with an OAI of 15–30 days had a nonsignificant 39% lesser chance of death. People with an OAI > 30 days had a 6% greater chance of death.
Paolucci et al, 2000 (19)	Prospective Case-Control		In a multiple logistic regression model for predictors of high response on BI score, OAI was significantly associated with a high therapeutic response ($P < 0.005$). Starting rehabilitation treatment within the first 20 days after the onset of stroke symptoms was significantly associated with a 1.8 increase on BI score or a 6-fold greater chance of having a high BI score. Conversely, starting rehabilitation 20 days after the onset of stroke symptoms is associated with a 1.64 decrease in BI score or a 5-fold greater risk of having a low BI score. Study participants were matched for age and BI score at admission.

Abbreviations: BI, Barthel Index; FIM, Functional Independence Measure; OAI, onset-to-admission interval; SREBR, Stroke Rehabilitation Evidence-Based Review.

Summaries of the results for each study are presented in Table 4.

Table 4: Summary of Results from SREBR Observational Studies

Author, Year	Study Design	Time Point of Outcome Evaluation (months)	Independent Variable OAI, days	Dependent	Mean (median) Score	B	95% CI (SE)	*P* value	OR (95% CI)
Hu et al, 2010 (13)[a,b]	P	D	C	BI	NA	−0.65	−1.2 to −0.10	0.02	NR
Huang et al, 2009 (14)[a]	R	(3) (6) (12)	C	BI	NA	−2.45 −2.49 −4.98	(0.5) (0.7) (0.9)	0.01 0.01 0.01	NR
Salter et al, 2006 (15)	R	D	0–15 16–30	FIM	106 95	NA	NA	< 0.01[c]	NR
Gagnon et al, 2006 (16)	R	D	< 20 20–40 > 41–70	FIM	(113) (105) (105)	N/A	N/A	0.08[d]	NR
Maulden et al, 2005 (17)[a]	P	D	C	FIM		−0.11[e] −0.15[f]	NR NR	0.004 < 0.001	NR NR
Musicco et al, 2003 (18)	P	D	≤ 7 8–14 15–30 > 30	Death		NA	NA	NA	1 0.9 (.51–1.6) 0.61 (.37–1.0) 1.06 (.66–1.7)
Paolucci et al, 2000 (19)[g]	P	D	OAI ≤ 20 OAI > 20	High BI Low BI		**1.81** **1.64**	(0.56 (0.8)	0.005 < 0.05	6.1 (2.03–18.4) 5.2 (1.1– 25.0)

Abbreviations: β, regression coefficient: BI, Barthel Index; C, continuous data; CI, confidence interval; D, discharge; FIM; Functional Independence Measure; NA, not applicable; NR, not reported; OAI, onset-to-admission interval; OR, odds ratio; P, prospective cohort; R, retrospective cohort; SREBR, Stroke Rehabilitation Evidence-Based Review; SE, standard error.

[a]Linear regression model.

[b]All strokes severity types.

[c]Age-adjusted comparison 0–15 days (BI score 101.5) vs. 16–30 days (BI score 77.3); higher BI score indicates greater independence.

[d]Comparison of discharge FIM scores across independent variable categories.

[e]Moderate stroke severity.

[f]Severe stroke severity.

[g]Logistic regression model.

A summary of the direction of effect is reported in Table 5. Of the 3 studies (13;14;19) that report on BI at discharge, a shorter OAI consistently predicts a higher BI (better function) at discharge. Of the 3 studies (15-17) that report on FIM score at discharge 2 report a shorter OAI predicts a significantly higher FIM score at discharge. (15;17) One study (16) did not find OAI was a significant predictor of FIM at discharge. The authors attribute this null effect to rehabilitation being initiated in the acute care setting with the participants in this study. (16)

Table 5: Summary of Direction of Effect

Author, Year	Outcome Measure	OAI, days (mean)	Direction of Effect
Hu et al, 2010 (13)	BI	(7)	Favours shorter OAI
Huang et al, 2009 (14)	BI	(8)	Favours shorter OAI
Salter et al, 2006 (15)	FIM	0–15	Favours shorter OAI
Gagnon et al, 2006 (16)	FIM	< 20–70	Null effect
Maulden et al, 2005 (17)	FIM	(14)	Favours shorter OAI
Musicco et al, 2003 (18)	Death	8–30	Null effect
Paolucci et al, 2000 (19)	BI	≤ 20	Favours shorter OAI

Abbreviations: BI, Barthel Index; FIM; Functional Independence Measure; OAI, onset-to-admission interval.

Limitations of Analysis

OAI may not be the only variable that predicts BI and FIM scores at discharge as well as death in the post-stroke period. It may also not be the variable that contributes the largest partial variance to the overall variance in a regression model. This rapid review reports on 2 relevant outcomes, death and dependency; however, there are other relevant outcomes including (but not limited to) complications and quality of life. These may be important for decision makers when evaluating the impact of OAI on stroke management.

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

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Appendices

Appendix 1: Literature Search Strategies

Stroke Mega – Timing of Rehabilitation – No Filter

Search dates: May 17-22, 2012
Databases searched: OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, EBSCO CINAHL, Centre for Reviews and Dissemination.

Database: Ovid MEDLINE(R) <1946 to May Week 2 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 16, 2012>, Embase <1980 to 2012 Week 19>
Search Strategy:
---
1 exp Stroke/ or exp brain ischemia/ (287165)
2 exp intracranial hemorrhages/ use mesz (50432)
3 exp brain hemorrhage/ use emez (70978)
4 exp stroke patient/ use emez (5976)
5 (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab. (337358)
6 or/1-5 (533181)
7 exp Rehabilitation/ or exp Rehabilitation Nursing/ (315936)
8 exp Rehabilitation Centers/ use mesz (11013)
9 exp rehabilitation center/ use emez (7708)
10 exp rehabilitation medicine/ or exp rehabilitation research/ use emez (4407)
11 exp rehabilitation care/ use emez (6643)
12 exp Stroke/rh [Rehabilitation] (12035)
13 exp Physical Therapy Modalities/ use mesz (111074)
14 exp physical medicine/ use emez (341473)
15 exp mobilization/ use emez (13582)
16 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*).ti,ab. (712734)
17 or/7-16 (1292451)
18 exp Time/ or exp early diagnosis/ (1589820)
19 exp Early Ambulation/ use mesz (1743)
20 exp dose response/ use emez (325275)
21 exp early intervention/ use emez (6043)
22 exp treatment duration/ or exp exercise intensity/ use emez (74069)
23 ((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) adj4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)).ti,ab. (85092)
24 or/18-23 (2047916)
25 6 and 17 and 24 (7408)
26 limit 25 to english language (6417)
27 limit 26 to yr="2000 -Current" (4682)
28 remove duplicates from 27 (3385)

CINAHL

#	Query	Results
S18	S6 and S10 and S17 Limiters - Published Date from: 20000101-20121231; English Language	1255
S17	S11 or S12 or S13 or S14 or S15 or S16	83867
S16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) N4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	11927
S15	(MH "Exercise Intensity")	4967
S14	(MH "Treatment Duration") OR (MH "Treatment Delay")	4564
S13	(MH "Dose-Response Relationship")	1675
S12	(MH "Early Ambulation") OR (MH "Early Intervention+")	7153
S11	(MH "Time+")	61769
S10	S7 or S8 or S9	226838
S9	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)	186389
S8	(MH "Rehabilitation Nursing") or (MH "Stroke/RH")	7704
S7	(MH "Rehabilitation+") OR (MH "Rehabilitation Centers+") OR (MH "Rehabilitation Patients")	127066
S6	S1 OR S2 OR S3 OR S4 OR S5	44299
S5	(MH "Stroke Patients")	1903
S4	stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain N2 isch?emia or cerebral N2 isch?emia or intracranial N2 hemorrhag* or brain N2 hemorrhag*	39724
S3	(MH "Intracranial Hemorrhage+")	4769
S2	(MH "Cerebral Ischemia+")	5517
S1	(MH "Stroke")	25767

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES	671
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES	180
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES	144
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or brain ajd2 isch?emia or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))	2188
5	#1 OR #2 OR #3 OR #4	2292
6	MeSH DESCRIPTOR Rehabilitation EXPLODE ALL TREES	1323

7	MeSH DESCRIPTOR Rehabilitation Nursing EXPLODE ALL TREES	7
8	MeSH DESCRIPTOR Rehabilitation Centers EXPLODE ALL TREES	70
9	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES WITH QUALIFIER RH	134
10	MeSH DESCRIPTOR Physical Therapy Modalities EXPLODE ALL TREES	1527
11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)	6719
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	7525
13	MeSH DESCRIPTOR time EXPLODE ALL TREES	1822
14	MeSH DESCRIPTOR Early Ambulation EXPLODE ALL TREES	22
15	MeSH DESCRIPTOR Early diagnosis EXPLODE ALL TREES	156
16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) adj4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	578
17	#13 OR #14 OR #15 OR #16	2527
18	#5 AND #12 AND #17	103
19	(#5 AND #12 AND #17) FROM 2000 TO 2012	88

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor **Stroke** explode all trees	4025
#2	MeSH descriptor **Brain Ischemia** explode all trees	1936
#3	MeSH descriptor **Intracranial Hemorrhages** explode all trees	1116
#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	16313
#5	(#1 OR #2 OR #3 OR #4)	18009
#6	MeSH descriptor **Rehabilitation** explode all trees	11919
#7	MeSH descriptor **Rehabilitation Nursing** explode all trees	32
#8	MeSH descriptor **Rehabilitation Centers** explode all trees	503
#9	MeSH descriptor **Stroke** explode all trees with qualifier: **RH**	1014
#10	MeSH descriptor **Physical Therapy Modalities** explode all trees	12459
#11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)	74282
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	80911

#13	MeSH descriptor **Time** explode all trees	48228
#14	MeSH descriptor **Early Diagnosis** explode all trees	490
#15	MeSH descriptor **Early Ambulation** explode all trees	257
#16	((time* or timing or interval* or delay* or early or initiation or onset or intens* or duration or augment* or dose-response or dose or dosing or dosage or frequency or enhance* or amount* or quantit*) NEAR/4 (rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*))	16018
#17	(#13 OR #14 OR #15 OR #16)	62212
#18	(**#5** AND **#12** AND **#17**), from 2000 to 2012	840

Appendix 2: Characteristics of Studies

Table A1: Characteristics of Studies Included for Analysis

Author, Year	Study Design	Objective	Country	Sample size, n	Mean Age, years	Study Population	Study Outcomes	OAI Mean (SD), days	Timing Variable
Bernhardt, 2008 (20)	RCT	To determine the safety and feasibility of VEM (< 24 hours after stroke) plus usual care compared with usual care	Australia	71	75	75% of study population was mild (NIHSS score 1–7) to moderate (NIHSS 8–16) stroke	Death, dependency at 3, 6, and 12 months after onset of stroke	NR	Continuous
Hu et al, 2010 (13)	Prospective Cohort	To investigate the predictors related to functional outcome at discharge from hospital	Taiwan	154	63	≥18 years of age with cerebro-vascular disease (ICD-9-CM) codes 430, 431, 434, 436	Prediction BI score at discharge	6.7 (6.7)	Continuous
Huang et al, 2009 (14)	Retrospective Cohort	To identify if earlier rehab therapy is better and other predictors for rehabilitation outcomes	Taiwan	76	60	People with first-ever stroke who received multidisciplinary inpatient rehabilitation that included physical and occupational therapy and continuous rehab at an outpatient department for at least 3 months	Prediction of BI scores post stroke	7.7	Continuous
Salter et al, 2006 (15)	Retrospective Cohort	To determine the effects of early versus delayed admission to stroke rehabilitation on functional outcome and length of stay	Canada	435	70	People with first-ever stroke admitted to a single specialized inpatient stroke rehabilitation program at a regional rehabilitation facility in Ontario within 150 days of first unilateral stroke	FIM	NR	Categorical < 30 days 31–150 days
Gagnon et al, 2006 (16)	Retrospective Cohort	To examine the influence of short, moderate and long OAIs on rehabilitation outcomes	Canada	120	71	People with first or recurrent stroke within 5 weeks of admission to study	FIM	31	Categorical Short < 20 days Moderate 20–40 days Long > 41–70 days

Author, Year	Study Design	Objective	Country	Sample size, n	Mean Age, years	Study Population	Study Outcomes	OAI Mean (SD), days	Timing Variable
Maulden et al, 2005 (17)	Prospective Cohort	To study the associations between days from onset of stroke symptoms to rehabilitation admission and rehabilitation outcomes	USA	969	67	People with moderate to severe stroke	Total FIM score	14	Continuous
Musicco et al, 2003 (18)	Prospective Cohort study	To determine how the time of initiation of rehabilitation influences the short and long-term outcomes of stroke patients	Italy	1716	70	People admitted for post-stroke rehabilitation to 20 rehabilitation hospitals and wards located throughout Italy	Death	> 7 days for 70% of study populatio n	Categorical ≤ 7 day 8–14 days 15–31 days > 30 days
Paolucci et al, 2000 (19)	Prospective Case-Control	To evaluation the specific influence of onset admission interval on rehabilitation results	Italy	135	70	People with first stroke admitted to inpatient rehabilitation	BI	> 21 days for 66% of study populatio n.	Categorical < 20 days > 21 days

Abbreviations: BI, Barthel Index; FIM, Functional Independence Measure; ICD-9-CM, *International Classification of Disease, 9th edition, Clinical Modification*; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; OAI, onset-to-admission interval; VEM, very early mobilization.

Appendix 3: Risk of Bias Observational Studies

Table A2: Risk of Bias Among Randomized Controlled Trials for the Comparison of Very Early Mobilization after Stroke Compared with Usual Care

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Bernhardt, 2001 (20)	No limitations	No limitations	No limitations	Limitations[a]	None

[a]Did not report the results of the secondary outcome of deterioration within the first 7 days according to the European Progressing Stroke Study definition.

Table A3: Risk of Bias Among Observational Trials for the Comparison of Onset-to-Admission Interval for Stroke Rehabilitation

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Complete Follow-Up	Adequate Control for Confounding
Hu et al, 2010 (13)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[a]
Huang et al, 2009 (14)	No Limitations	No Limitations	No Limitations	Limitations[b]	**Limitations**[c]
Salter et al, 2006 (15)	No Limitations	No Limitations	No Limitations	No Limitations	**Limitations**[d]
Gagnon et al, 2006 (16)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[e]
Maulden et al, 2005 (17)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[f]
Musicco et al, 2003 (18)	No Limitations	No Limitations	No Limitations	No Limitations	**Limitations**[g]
Paolucci et al, 2000 (19)	No Limitations	No Limitations	No Limitations	Limitations[h]	No Limitations[i]

Abbreviations: BI, Barthel Index; CI, confidence interval; FIM, Functional Independence Measure; NIHSS, National Institute of Health Stroke Scale; OAI, onset-to-admission interval; OR, odds ratio. .

[a]Regression model adjusted for NIHSS, rehabilitation intensity, BI admission score and OAI.

[b]n = 76 participants of which data was available for n = 73 at 1 months, 62 at 3 months, 47 at 6 months, and 21 at 1 year.

[c]Collinearity among potential variables not reported as evaluated, regression model for outcome at 3 months adjusted for initial BI score, number of occupational therapy units received, age, OAI, infarction stroke type, Brunnstrom's motor recovery stages for proximal upper limb and length of stay, regression model for outcome at 6 months included the previously stated independent factors for regression analysis at 3 months as well as number of physiotherapy units received added with the number of occupational therapy units received, regression model at 1 year included OAI and infarction stroke type only.

[d]Adjusted analysis for age but not for baseline FIM score or stroke severity.

[e]Study participants matched on stroke severity, age, and gender; no adjustment for BI on admission.

[f]Regression model for people with moderate stroke adjusted for OAI, age, gender, admission motor RIM score, admission cognitive FIM score, maximum severity score, employed prior to admission, ambulatory prior to admission, regression model for people with severe stroke adjusted for OAI, age, race, side of lesion, admission motor FIM score, admission cognitive FIM score, maximum severity score, employed prior to admission, activities of daily living independent prior to admission, and rehabilitation length of stay.

[g]Logistic regression analysis on OAI adjusted for disability severity (FIM score) or age. Variables individually entered in the logistic regression model and 95% CIs of OR calculated. No adjustment of significance level was made to account for multiple comparisons.

[h]The 3 OAI groups differed significantly in percentage of dropouts with 17.8% of dropouts in the short OAI group compared with 6.67% in the medium OAI group and 2.22% in the long OAI group ($P < 0.05$).

[i]Logistic regression model was adjusted for age, sex, etiology of stroke, side of motor deficit, severity of stroke, OAI, and presence of post-stroke seizures, hemineglect, Broca's aphasia, Wenicke's aphasia, and global aphasia.

Appendix 4: GRADE Tables

Table A4: GRADE Evidence Profile for Studies Determining Optimal Onset-to-Admission Interval for Stroke Rehabilitation

Number of Studies, Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Example Outcome							
RCTs or observational	No serious limitations Serious limitations (−1)[a] Very serious limitations (−2)[a]	No serious limitations Serious limitations (−1)[a] Very serious limitations (−2)[a]	No serious limitations Serious limitations (−1)[a] Very serious limitations (−2)[a]	No serious limitations Serious limitations (−1)[a] Very serious limitations (−2)[a]	Undetected Likely (−1)[a] Very likely (−2)[a]	Large magnitude of effect (+1) Dose-response gradient (+1) All plausible confounding increases confidence in estimate (+1) Other considerations (+1)	⊕⊕⊕⊕ High ⊕⊕⊕ Moderate ⊕⊕ Low ⊕ Very Low
Outcome Death							
1 RCT Bernhardt et al, 2001 (20)	None	NA[a]	None	Serious[b] Limitations	Likely[c] (−1)	None	⊕⊕ Low
Outcome Dependency							
1 RCT Bernhardt et al, 2001 (20)	None	NA[a]	None	Serious[b] Limitations	Likely[c] (−1)	None	⊕⊕ Low
Outcome Death							
1 Observational Musicco et al, 2003 (18)	Serious[d]	NA[a]	None	Serious[e]	Undetected	None	⊕ Very Low
Outcome BI Index at Discharge							
3 Observational Hu et al, 2010 (13) Huang et al, 2009 (14) Paolucci et al, 2000 (19)	None[f]	None	None	None	Undetected	None	⊕ Very Low
Outcome FIM Index at Discharge							
3 Observational Salter et al, 2006 (15)	None	None[g]	None	Serious[h]	None	None	⊕ Very Low

Gagnon et al, 2006 (16)
Maulden et al, 2005 (17)

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

[a]Only 1 study, cannot assess consistency.

[b]Optimal information size criterion not met.

[c]Rapidly growing body of Chinese literature that is difficult to access.

[d]No adjustment for multiple comparisons in study.

[e]Confidence intervals span appreciable risks and benefits.

[f]Significant limitations in loss to follow-up, and confounding with 2 studies (Gagnon et al [16] and Salter et al [15]) that did not adjust analysis for possible confounding variables.

[g]Two studies (Maulden et al [17] and Salter et al [15]) found shorter OAI to significantly predict FIM score while the third study (Gagnon et al [16]) found a null effect. This null effect was explained as confounding due to early rehabilitation therapy beginning in the acute phase of this study therefore no downgrading was applied.

[h]Variances not reported for means, medians, or coefficient and precision difficult to assess.

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