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Optimal Onset-to-Admission Interval for Inpatient Stroke Rehabilitation: A Rapid Review

Health Quality Ontario

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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 This rapid review may be superseded by an updated publication on the same topic.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.

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

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.

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 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 stroke or a TIA. (3) The mean age was 72.3 years, and over half were 66 to 84 years of age. Of these, 37.0% presented with a TIA; 4.9% with an ischemic stroke, and 8.5% with hemorrhagic stroke; 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)

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. (4) Post-stroke rehabilitation interventions have been used to increase functional status and quality of life in the weeks after a stroke. (4) 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 stroke unit have reduced rates of mortality, institutionalization, and dependency. (5) 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 (6) 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)

Ontario Context

Approximately 20,000 Ontarians per year experience stroke. Of these, 3,000 are admitted to inpatient rehabilitation. (8) 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; the regional variation in wait times for admission to rehabilitation was 6 days. (3) Of people eligible for inpatient stroke rehabilitation in Ontario, 19% remained in an acute care facility longer than necessary while waiting for access to a rehabilitation bed in an inpatient facility. (9)

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. (10) 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. (10) For more detailed information, please refer to the latest series of GRADE articles. (10)

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 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. (11)

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. (5;12) Neither review used GRADE Working Group criteria to evaluate the body of evidence.

Very Early Mobilization

A systematic review by Bernhardt et al (12) 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. (13) 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 were 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 Institutes of Health Stroke Scale score (mild score: 1–7; moderate score 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. (14) 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 recommendations on the practice. (12) 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. (12) 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. One limitation of this study is that the very early group is compared to a usual care group that gets mobilized at 2 days. Mobilization at 2 days may not be the standard of care in Ontario. Greater directness for the Ontario context would have been achieved if the comparison group was mobilized at a later time. The GRADE level for the body of evidence for each outcome is low (Appendix 4).

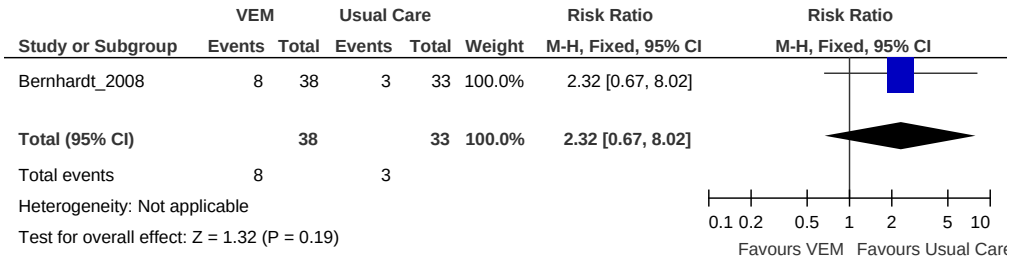

Figure 1: Forest Plot of Death at 3 Months Post Stroke

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

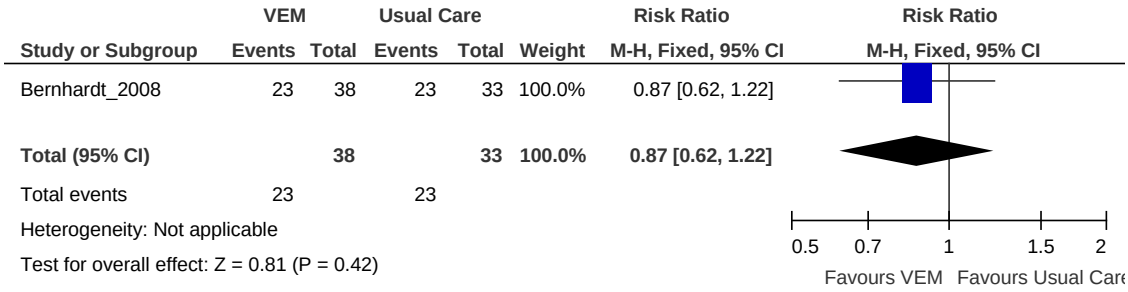

Figure 2: Forest Plot of Dependency at 3 Months Post Stroke

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. (5) The AMSTAR score for this review was 10. (13) 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 (15)	Huang et al, 2009 (16)	Salter et al, 2006 (17)	Gagnon et al, 2006 (6)	Maulden et al, 2005 (18)	Musicco et al, 2003 (19)	Paolucci et al, 2000 (20)
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 (15)	Prospective Cohort	Regression	In a multiple linear regression model for predictors of BI at discharge from inpatient rehabilitation, time to the 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 (16)	Retrospective Cohort	Regression	In a stepwise multivariate linear regression for predictors of BI at various time points post stroke, time to the 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 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 (17)	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 (6)	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 (18)	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 (19)	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.

Study	Design	Analysis	Outcome
Paolucci et al, 2000 (20)	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	β	95% CI (SE)	*P* value	OR (95% CI)
Hu et al, 2010 (15)[a,b]	P	D	C	BI	NA	−0.65	−1.2 to −0.10	0.02	NR
Huang et al, 2009 (16)[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 (17)	R	D	0–15 16–30	FIM	106 95	NA	NA	< 0.01[c]	NR
Gagnon et al, 2006 (6)	R	D	< 20 20–40 > 41–70	FIM	(113) (105) (105)	N/A	N/A	0.08[d]	NR
Maulden et al, 2005 (18)[a]	P	D	C	FIM		−0.11[e] −0.15[f]	NR NR	0.004 < 0.001	NR NR
Musicco et al, 2003 (19)	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 (20)[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 that report on BI at discharge, (15;16;20) a shorter OAI consistently predicts a higher BI (better function) at discharge. Of the 3 studies that report on FIM score at discharge (6;17;18), 2 report that a shorter OAI predicts a significantly higher FIM score at discharge. (17;18) One study did not find that OAI was a significant predictor of FIM at discharge (6). The authors attribute this null effect to rehabilitation being initiated in the acute care setting. (6)

Table 5: Summary of Direction of Effect

Author, Year	Outcome Measure	OAI, days (mean)	Direction of Effect
Hu et al, 2010 (15)	BI	(7)	Favours shorter OAI
Huang et al, 2009 (16)	BI	(8)	Favours shorter OAI
Salter et al, 2006 (17)	FIM	0–15	Favours shorter OAI
Gagnon et al, 2006 (6)	FIM	< 20–70	Null effect
Maulden et al, 2005 (18)	FIM	(14)	Favours shorter OAI
Musicco et al, 2003 (19)	Death	8–30	Null effect
Paolucci et al, 2000 (20)	BI	≤ 20	Favours shorter OAI

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

Conclusion

There is evidence of very low quality that an earlier onset of rehabilitation post stroke (onset of rehabilitation before 14 days) results in increased independency and functionality compared with a later start time for stroke rehabilitation. . Until better quality evidence is available the timing of rehabilitation ought to be initiated as soon as the patient is ready.

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, costs of acute and rehabilitation hospital care, and quality of life. These may be important for decision makers when evaluating the impact of OAI on stroke management.

Acknowledgements

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Appendices

Appendix 1: Literature Search Strategies

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:

#	Searches
1	exp Stroke/ or exp brain ischemia/
2	exp intracranial hemorrhages/ use mesz
3	exp brain hemorrhage/ use emez
4	exp stroke patient/ use emez
5	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain adj2 isch?emia) or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)).ti,ab.
6	or/1-5
7	exp Rehabilitation/ or exp Rehabilitation Nursing/
8	exp Rehabilitation Centers/ use mesz
9	exp rehabilitation center/ use emez
10	exp rehabilitation medicine/ or exp rehabilitation research/ use emez
11	exp rehabilitation care/ use emez
12	exp Stroke/rh [Rehabilitation]
13	exp Physical Therapy Modalities/ use mesz
14	exp physical medicine/ use emez
15	exp mobilization/ use emez
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.
17	or/7-16
18	exp Time/ or exp early diagnosis/
19	exp Early Ambulation/ use mesz
20	exp dose response/ use emez
21	exp early intervention/ use emez
22	exp treatment duration/ or exp exercise intensity/ use emez
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.

24 or/18-23

25 6 and 17 and 24

26 limit 25 to english language

27 limit 26 to yr="2000 -2012"

28 remove duplicates from 27

CINAHL

#	Query
S1	(MH "Stroke")
S2	(MH "Cerebral Ischemia+")
S3	(MH "Intracranial Hemorrhage+")
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*))
S5	(MH "Stroke Patients")
S6	S1 OR S2 OR S3 OR S4 OR S5
S7	(MH "Rehabilitation+") OR (MH "Rehabilitation Centers+") OR (MH "Rehabilitation Patients")
S8	(MH "Rehabilitation Nursing") or (MH "Stroke/RH")
S9	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)
S10	S7 or S8 or S9
S11	(MH "Time+")
S12	(MH "Early Ambulation") OR (MH "Early Intervention+")
S13	(MH "Dose-Response Relationship")
S14	(MH "Treatment Duration") OR (MH "Treatment Delay")
S15	(MH "Exercise Intensity")
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*))
S17	S11 OR S12 OR S13 OR S14 OR S15 OR S16
S18	S6 AND S10 AND S17
S19	S6 AND S10 AND S17 Limiters - Published Date from: 20000101-20121231; English Language

CRD

Line	Search
1	MeSH DESCRIPTOR stroke EXPLODE ALL TREES
2	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES
3	MeSH DESCRIPTOR intracranial hemorrhages EXPLODE ALL TREES
4	((stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain adj2 isch?emia) or (cerebral adj2 isch?emia) or (intracranial adj2 hemorrhag*) or (brain adj2 hemorrhag*)))
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Rehabilitation EXPLODE ALL TREES
7	MeSH DESCRIPTOR Rehabilitation Nursing EXPLODE ALL TREES
8	MeSH DESCRIPTOR Rehabilitation Centers EXPLODE ALL TREES
9	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES WITH QUALIFIER RH
10	MeSH DESCRIPTOR Physical Therapy Modalities EXPLODE ALL TREES
11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11
13	MeSH DESCRIPTOR time EXPLODE ALL TREES
14	MeSH DESCRIPTOR Early Ambulation EXPLODE ALL TREES
15	MeSH DESCRIPTOR Early diagnosis EXPLODE ALL TREES
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*))
17	#13 OR #14 OR #15 OR #16
18	#5 AND #12 AND #17
19	#18 FROM 2000 TO 2012

Wiley Cochrane

ID	Search
#1	MeSH descriptor: [Stroke] explode all trees
#2	MeSH descriptor: [Brain Ischemia] explode all trees
#3	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#4	(stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain near/2 isch?emia) or (cerebral near/2 isch?emia) or (intracranial near/2 hemorrhag*) or (brain near/2 hemorrhag*)):ti or (stroke or tia or transient ischemic attack or cerebrovascular apoplexy or cerebrovascular accident or cerebrovascular infarct* or brain infarct* or CVA or (brain near/2 isch?emia) or (cerebral near/2 isch?emia) or (intracranial near/2 hemorrhag*) or (brain near/2 hemorrhag*)):ab
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Rehabilitation] explode all trees
#7	MeSH descriptor: [Rehabilitation Nursing] explode all trees
#8	MeSH descriptor: [Rehabilitation Centers] explode all trees
#9	MeSH descriptor: [Stroke] explode all trees and with qualifiers: [Rehabilitation - RH]
#10	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#11	(rehabilitat* or habilitat* or movement therap* or physiotherap* or physical therap* or exercis* or occupational therap* or mobilization or mobilisation or strength train*)
#12	#6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Time] explode all trees
#14	MeSH descriptor: [Early Diagnosis] explode all trees
#15	MeSH descriptor: [Early Ambulation] explode all trees
#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*))
#17	#13 or #14 or #15 or #16
#18	#5 and #12 and #17 from 2000 to 2012

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 (14)	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 (15)	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 (16)	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

Author, Year	Study Design	Objective	Country	Sample size, n	Mean Age, years	Study Population	Study Outcomes	OAI Mean (SD), days	Timing Variable
Salter et al, 2006 (17)	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 (6)	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
Maulden et al, 2005 (18)	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

Author, Year	Study Design	Objective	Country	Sample size, n	Mean Age, years	Study Population	Study Outcomes	OAI Mean (SD), days	Timing Variable
Musicco et al, 2003 (19)	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 population	Categorical ≤ 7 day 8–14 days 15–31 days > 30 days
Paolucci et al, 2000 (20)	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 population.	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, 2008 (14)	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 (15)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[a]
Huang et al, 2009 (16)	No Limitations	No Limitations	No Limitations	Limitations[b]	Limitations[c]
Salter et al, 2006 (17)	No Limitations	No Limitations	No Limitations	No Limitations	Limitations[d]
Gagnon et al, 2006 (6)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[e]
Maulden et al, 2005 (18)	No Limitations	No Limitations	No Limitations	No Limitations	No Limitations[f]
Musicco et al, 2003 (19)	No Limitations	No Limitations	No Limitations	No Limitations	Limitations[g]
Paolucci et al, 2000 (20)	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 FIM 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 (14)	None	NA[a]	Serious limitations[i]	Serious[b] Limitations	Likely[c] (−1)	None	⊕ Very Low
Outcome Dependency							
1 RCT Bernhardt et al, 2001 (14)	None	NA[a]	Serious limitations[i]	Serious[b] Limitations	Likely[c] (−1)	None	⊕ Very Low
Outcome Death							
1 Observational Musicco et al, 2003 (19)	Serious[d]	NA[a]	None	Serious[e]	Undetected	None	⊕ Very Low
Outcome BI Index at Discharge							
3 Observational Hu et al, 2010 (15) Huang et al, 2009 (16) Paolucci et al, 2000 (20)	None[f]	None	None	None	Undetected	None	⊕ Very Low
Outcome FIM Index at Discharge							

3 Observational Salter et al, 2006 (17) Gagnon et al, 2006 (6) Maulden et al, 2005 (18)	None	None[g]	None	Serious[h]	None	None	⊕ Very Low

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 [(6)] and Salter et al (17)) that did not adjust analysis for possible confounding variables.
[g]Two studies (Maulden et al (18) and Salter et al (17)) found shorter OAI to significantly predict FIM score while the third study (Gagnon et al [(6)) 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.
[i] study compares very early mobilization to persons who are mobilized within 2 days post stroke. This comparator group is not generalizable to the Ontario context.

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