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Very early versus delayed mobilisation after stroke (Review)

Langhorne P, Collier JM, Bate PJ, Thuy MNT, Bernhardt J

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[Intervention Review]

Very early versus delayed mobilisation after stroke

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ABSTRACT

Background

Very early mobilisation (VEM) is performed in some stroke units and recommended in some acute stroke clinical guidelines. However, it is unclear whether very early mobilisation independently improves outcome after stroke.

Objectives

To determine whether very early mobilisation (started as soon as possible, and no later than 48 hours after onset of symptoms) in people with acute stroke improves recovery (primarily the proportion of independent survivors) compared with usual care.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched 31 July 2017). We also systematically searched 19 electronic databases including; CENTRAL; 2017, Issue 7 in the *Cochrane Library* (searched July 2017), MEDLINE Ovid (1950 to August 2017), Embase Ovid (1980 to August 2017), CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to August 2017) , PsycINFO Ovid (1806 to August 2017), AMED Ovid (Allied and Complementary Medicine Database), SPORTDiscus EBSCO (1830 to August 2017). We searched relevant ongoing trials and research registers (searched December 2016), the Chinese medical database, Wanfangdata (searched to November 2016), and reference lists, and contacted researchers in the field.

Selection criteria

Randomised controlled trials (RCTs) of people with acute stroke, comparing an intervention group that started out-of-bed mobilisation within 48 hours of stroke, and aimed to reduce time-to-first mobilisation, with or without an increase in the amount or frequency (or both) of mobilisation activities, with usual care, where time-to-first mobilisation was commenced later.

Data collection and analysis

Two review authors independently selected trials, extracted data, assessed risk of bias, and applied the GRADE approach to assess the quality of the evidence. The primary outcome was death or poor outcome (dependency or institutionalisation) at the end of scheduled follow-up. Secondary outcomes included death, dependency, institutionalisation, activities of daily living (ADL), extended ADL, quality of life, walking ability, complications (e.g. deep vein thrombosis), patient mood, and length of hospital stay. We also analysed outcomes at three-month follow-up.

Main results

We included nine RCTs with 2958 participants; one trial provided most of the information (2104 participants). The median (range) delay to starting mobilisation after stroke onset was 18.5 (13.1 to 43) hours in the VEM group and 33.3 (22.5 to 71.5) hours in the usual care group.

The median difference within trials was 12.7 (4 to 45.6) hours. Other differences in intervention varied between trials; in five trials, the VEM group were also reported to have received more time in therapy, or more mobilisation activity.

Primary outcome data were available for 2542 of 2618 (97.1%) participants randomized and followed up for a median of three months. VEM probably led to similar or slightly more deaths and participants who had a poor outcome, compared with delayed mobilisation (51% versus 49%; odds ratio (OR) 1.08, 95% confidence interval (CI) 0.92 to 1.26; P = 0.36; 8 trials; moderate-quality evidence). Death occurred in 7% of participants who received delayed mobilisation, and 8.5% of participants who received VEM (OR 1.27, 95% CI 0.95 to 1.70; P = 0.11; 8 trials, 2570 participants; moderate-quality evidence), and the effects on experiencing any complication were unclear (OR 0.88; 95% CI 0.73 to 1.06; P = 0.18; 7 trials, 2778 participants; low-quality evidence). Analysis using outcomes collected only at three-month follow-up did not alter the conclusions.

The mean ADL score (measured at end of follow-up, with the 20-point Barthel Index) was higher in those who received VEM compared with the usual care group (mean difference (MD) 1.94, 95% CI 0.75 to 3.13, P = 0.001; 8 trials, 9 comparisons, 2630/2904 participants (90.6%); low-quality evidence), but there was substantial heterogeneity (93%). Effect sizes were smaller for outcomes collected at three-month follow-up, rather than later.

The mean length of stay was shorter in those who received VEM compared with the usual care group (MD -1.44, 95% CI -2.28 to -0.60, P = 0.0008; 8 trials, 2532/2618 participants (96.7%); low-quality evidence). Confidence in the answer was limited by the variable definitions of length of stay. The other secondary outcome analyses (institutionalisation, extended activities of daily living, quality of life, walking ability, patient mood) were limited by lack of data.

Sensitivity analyses by trial quality: none of the outcome conclusions were altered if we restricted analyses to trials with the lowest risk of bias (based on method of randomization, allocation concealment, completeness of follow-up, and blinding of final assessment), or information about the amount of mobilisation.

Sensitivity analysis by intervention characteristics: analyses restricted to trials where the mean VEM time-to-first mobilisation was less than 24 hours, showed an odds of death of 1.35 (95% CI 0.99 to 1.83; P = 0.06; I^2 = 25%; 5 trials). Analyses restricted to the trials that clearly reported a more prolonged out-of-bed activity showed a similar primary outcome (OR 1.14; 0.96 to 1.35; P = 0.13; I^2 = 28%; 5 trials), and odds of death (OR 1.27; 0.93 to 1.73; P = 0.13; I^2 = 0%; 4 trials) to the main analysis.

Exploratory network meta-analysis (NMA): we were unable to analyze by the amount of therapy, but low-quality evidence indicated that time-to-first mobilisation at around 24 hours was associated with the lowest odds of death or poor outcome, compared with earlier or later mobilisation.

Authors' conclusions

VEM, which usually involved first mobilisation within 24 hours of stroke onset, did not increase the number of people who survived or made a good recovery after their stroke. VEM may have reduced the length of stay in hospital by about one day, but this was based on low-quality evidence. Based on the potential hazards reported in the single largest RCT, the sensitivity analysis of trials commencing mobilisation within 24 hours, and the NMA, there was concern that VEM commencing within 24 hours may carry an increased risk, at least in some people with stroke. Given the uncertainty around these effect estimates, more detailed research is still required.

PLAIN LANGUAGE SUMMARY

Very early versus delayed mobilisation after stroke

Review question
Does very early and active mobilisation improve recovery after stroke compared with more delayed mobilisation?

Background
Care in a stroke unit is recommended for people soon after a stroke, and results in an improved chance of surviving, returning home, and regaining independence. Very early mobilisation (helping people to get up out of bed very early, and more often after the onset of stroke symptoms) is performed in some stroke units, and is recommended in many acute stroke clinical guidelines. However, the impact of very early mobilisation on recovery after stroke is not clear.

Search date
This review is up-to-date to July 2017.

Study characteristics
This review identified nine trials (2958 participants), although one trial (2104 participants) provided most of the information. On average, very early mobilisation participants started mobilisation 18.5 hours after their stroke, compared with 33.3 hours in the usual care group. In five trials, the very early mobilisation group were also known to have spent more time per day in therapy, or participated in a mobilisation activity.

Main results

Very early mobilisation did not increase the number of people who survived or made a good recovery after their stroke. There was a suggestion that very early mobilisation may reduce the length of stay in hospital by about one day. However, results from the single largest trial, and from an analysis of trials that started mobilising participants very early, raised the concern that starting intensive mobilisation within 24 hours of stroke may carry some increased risk, at least for some people with stroke. This potential risk needs to be clarified.

Quality of the evidence

Overall, the main results were supported by moderate-quality evidence overall, but low-quality evidence backed length of hospital stay and activities of daily living.

Summary of findings for the main comparison.

Very early mobilisation versus delayed mobilisation						
Patient or population: adults with acute stroke **Settings:** stroke unit or acute ward **Intervention:** very early mobilisation (VEM) **Comparison:** delayed mobilisation						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Delayed mobilisation	**Very early mobilisation**				
Death or a poor outcome (median 3-month follow-up)	**Medium risk population**		**OR 1.08** (0.92 to 1.26)	**2542 (8)**	⊕⊕⊕⊖ moderate [a]	Largest trial (2104 participants) found increased risk of death or poor outcome with VEM
	486 per 1000	**507 per 1000 (465 to 544)**				
Death (median 3-month follow-up)	**Medium risk population**		**OR 1.27** (0.95 to 1.70)	**2561 (8)**	⊕⊕⊕⊖ moderate [a]	Sensitivity analysis suggested increased risk of death in trials with earlier onset of VEM
	68 per 1000	**85 per 1000 (65 to 112)**				
Death or dependence (modified Rankin score 3 to 6; median 3-month follow-up)	**Medium risk population**		**OR 1.08** (0.92 to 1.26)	**2542 (8)**	⊕⊕⊕⊖ moderate [a]	Largest trial found increased risk of death or dependency with VEM
	486 per 1000	**507 per 1000 (465 to 544)**				
Activities of daily living (ADL) (Barthel Index score 0 to 20; lower = 0; median 3-month follow-up)	The mean Barthel Index scores across control groups ranged from 14.2 to 18.1.	The mean Barthel Index score in the intervention groups was on average **1.94 points**	**MD 1.94 higher** (0.75 to 3.13 higher)	**2630 (8)**	⊕⊕⊖⊖ low [a, b]	Higher rate of missing data

		higher (0.75 higher to 3.13 higher).				
Subjective Health Status score (Assessment of Quality of Life Score 0 to 1; lower = 0; end of scheduled follow-up)	The mean Assessment of Quality of Life (AQoL) score in the control group was 0.306	The mean AQoL score in the intervention group was on average **0.07 points higher** (0.1 lower to 0.23 higher)	**MD 0.07 higher** (0.1 lower to 0.23 higher)	**68 (1)**	⊕⊝⊝⊝ very low [a, b, c]	Higher rate of missing data Data from one trial only
Any complication: participants who experience at least one complication (median 3-month follow-up)	**Medium risk population**		**OR 0.88** (0.73 to 1.06)	**2778 (6)**	⊕⊕⊕⊝ low [a, c]	Uncertain blinding at follow-up
	224 per 1000	**200 per 1000** (174 to 234)				
Length of acute hospital stay (days)	The mean length of stay across control groups ranged from 9.8 to 14.9 days.	The mean length of stay in the intervention groups was, on average, **1.44 days less** (2.28 days less to 0.60 day less)	**MD 1.44 lower** (2.28 lower to 0.60 lower)	**2551 (8)**	⊕⊕⊝⊝ low [a, b]	Different definitions and imprecise measures of length of stay were reported Result largely depends on two small trials with small SDs

*The basis for the **assumed risk** (e.g. the mean control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** odds ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Downgraded for potential risk of performance bias.
[b] Downgraded for unexplained heterogeneity.
[c] Downgraded for imprecision.

BACKGROUND

Description of the condition

Stroke presents a major global public health challenge, with over five million people dying from stroke each year, and many more living with chronic disability (Murray 2012). We know that treatment in an organised multidisciplinary stroke unit (compared with treatment in a general medical ward) reduces the odds of being dead or disabled at 12 months post stroke (SUTC 2013). However, relatively little is known about which components of acute stroke unit care may be responsible for better outcomes (Langhorne 2012). Early rehabilitation (in particular early mobilisation) is described as an important feature of stroke unit care, but there is only limited information about what early rehabilitation entails and who provides it (Langhorne 2012). In addition to the uncertainties surrounding the optimal amount of rehabilitation that can be provided early after stroke, exactly how early rehabilitation should start is controversial.

Description of the intervention

Early mobilisation (getting people up and out of bed and sitting, standing, and walking early after stroke) is an established feature of acute stroke unit care, particularly in many Scandinavian hospitals (Indredavik 1999). In other parts of the world, patients may be restricted to bed for some days before mobilisation is allowed (Diserens 2006). In some cases, these differences in practice reflect concerns about the possibility that early mobilisation may have a detrimental effect on the vulnerable ischaemic penumbra (Diserens 2006), although there is little evidence to support this view (Bernhardt 2007; Bernhardt 2015), while in other cases, they are likely to reflect historical practices.

How the intervention might work

The biological rationale for early mobilisation is based on three lines of argument: 1) there is evidence that bedrest has a harmful impact across many conditions, and is likely to slow recovery (Allen 1999; Mutin-Carino 2014); 2) some of the most common and serious complications after stroke are those related to immobility (Langhorne 2000); and 3) current concepts of biological recovery after brain injury suggest a narrow window of opportunity for brain plasticity and repair (Murphy 2009). We know that the routine day of most acute stroke patients is largely inactive, so introducing frequent training out of bed could reduce the risk of complications of immobility (Bernhardt 2004; Bernhardt 2015). Also, if the brain does indeed remodel itself based on experience (Johansson 2000; Krakauer 2012), then early task-specific training may well contribute to improving recovery (Pekna 2012).

However, there are also concerns about potential harm of early mobilisation, particularly in the first 24 hours after stroke onset (Bernhardt 2004; Skarin 2011). These concerns include haemodynamic considerations: whether raising the person's head early after stroke will impair cerebral blood flow and cerebral perfusion (Skarin 2011). Alternatively, in the case of intracerebral haemorrhage, whether early mobilisation will increase the risk of inducing further bleeding (Olavarria 2014). As a result of these theoretical concerns, some clinicians have advocated initial bedrest for people with stroke (Skarin 2011). This uncertainty about the best approach stimulated a large cluster-randomised trial that explored the impact of head postioning in people with acute stroke (Muñoz-Venturelli 2015). This trial found no clear difference in outcomes for people nursed flat for the first 24 hours after stroke versus those nursed with their head up, and allowed to mobilise to the toilet (Anderson 2017).

Why it is important to do this review

Although very early mobilisation (VEM) has been recommended in a number of acute stroke clinical guidelines (Adams 2003; Bernhardt 2015; NSF 2007), only indirect evidence currently supports these recommendations (Indredavik 1999). It is not known whether VEM independently improves outcome after stroke.

OBJECTIVES

To determine whether very early mobilisation (started as soon as possible, and no later than 48 hours after onset of symptoms) in people with acute stroke improves recovery (primarily the proportion of independent survivors) compared with usual care.

METHODS

Criteria for considering studies for this review

Types of studies

We sought all randomized trials, with or without blinding, of VEM within 48 hours of symptom onset compared with more delayed, usual care (i.e. normal practice or no routine intervention).

Types of participants

Participants in trials had to be adults with a definite clinical diagnosis of stroke (focal neurological deficit of cerebrovascular origin), and could be mobilised within 48 hours of stroke onset. There were no age restrictions.

Types of interventions

We defined VEM as any intervention delivered with the aim of reducing the time from stroke onset to first mobilisation (first out-of-bed episode), which may have included increasing the amount of out-of-bed physical activity (e.g. participation in activities of daily living (ADLs), such as walking to the toilet, transferring on and off the toilet, sitting out of bed, standing, and walking). Any form of VEM was considered, regardless of the number and discipline of staff assisting, and the dose or duration of the intervention. We defined usual care as the usual mobilisation practice.

Types of outcome measures

The aim was to identify all outcomes of interest at the end of scheduled follow-up, and also (where available) at three-month follow-up.

Primary outcomes

Death or a poor outcome: the number of participants who died or had a poor outcome at the end of scheduled follow-up (in preferred order, this was defined as: remained dependent (modified Rankin Score (mRS) 3 to 5, or Barthel score < 15, or equivalent), or required admission to institutional care. We defined institutional care as care provided in a residential home, nursing home, or hospital at follow-up.

Secondary outcomes

- Death: number of deaths from any cause

- Death or dependence: the number of participants dead or physically dependent (mRS 3 to 5, or equivalent)
- Death or requiring institutional care: we defined institutional care as care provided in a residential home, nursing home, or hospital at follow-up.
- Performance in activities of daily living (ADL): using a recognised ADL score
- Performance in extended activities of daily living (community and domestic activities): using a recognised extended ADL score
- Patient subjective health status or quality of life score
- Ability to walk: walking unassisted (without help from another person), reported alone, or as a component of a functional mobility scale
- Mobility score: using a recognised mobility score
- Complications (adverse events): number or severity (or both) of complications (adverse events), including deep vein thrombosis (DVT), pulmonary embolism (PE), incidence and grade of pressure sores (using standardized grading scale), number of incontinent episodes over 24 hours, severity of incontinence, chest infection, falls, and physiological variables (blood pressure, oxygen, temperature) recorded
- Type of complication (adverse events): categorised as complications of immobility (DVT, PE, incidence and grade of pressure sores (using standardized grading scale), chest infection, urinary tract infection, falls), and other complications
- Patient mood: using a recognised measure of mood
- Length of stay in acute hospital (recorded in days)

Search methods for identification of studies

See the Cochrane Stroke Group Trials Register. We aimed to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress). We arranged translation of relevant articles where required.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Cochrane Stroke Group Information Specialist on 31 July 2017. In addition, we systematically searched the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7) in the *Cochrane Library* (searched August 2017; Appendix 1);
- MEDLINE Ovid (1950 to August 2017; Appendix 2);
- Embase Ovid (1980 to August 2017; Appendix 3);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to August 2017; Appendix 4);
- PsycINFO Ovid (1806 to August 2017; Appendix 5);
- AMED Ovid (Allied and Complementary Medicine Database; 1985 to August 2017; Appendix 6);
- SPORTDiscus EBSCO (1830 to August 2017; Appendix 7);
- Science Citation Index Expanded (1900 to August 2017; Appendix 8);
- Social Sciences Citation Index (1956 to August 2017);
- Arts and Humanities Citation Index (1975 to August 2017);
- PEDro (Physiotherapy Evidence Database (www.pedro.fhs.usyd.edu.au/; 1929 to December 2006);
- REHABDATA (National Rehabilitation Information Centre (www.naric.com/?q=en/REHABDATA; 1956 to November 2016);
- CIRRIE (Center for International Rehabilitation Research Information and Exchange (cirrie.buffalo.edu/; 1990 to November 2016);
- OTSeeker (searched to November 2016);
- Wan Fang Database (www.wanfangdata.com/; searched to November 2016);
- British Association of Occupational Therapists' Library Collection (including Thesis Collection; searched to November 2016);
- ProQuest Dissertations and Theses — Global (formerly Index to UK Theses; searched to November 2016).

We used the search strategy for MEDLINE, and with the assistance of the Cochrane Stroke Group Information Specialist, modified it to suit other databases (Appendix 2).

We searched the following ongoing trials and research registers.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (ClinicalTrials.gov; searched December 2016);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP'; apps.who.int/trialsearch; searched December 2016);
- ISRCTN Registry (www.isrctn.com; formerly the Meta Register of Controlled Trials (mRCT): www.controlled-trials.com/mrct/; searched December 2016);
- UK Department of Health Research Findings Register (ReFeR and latterly www.isrctn.com/).

Searching other resources

- We originally handsearched all available years of the following journals (these were not updated after 2006 in view of the increased sensitivity of our other search strategies).
  - *Advances in Occupational Medicine and Rehabilitation* (1996 to 1999);
  - *Advances in Clinical Neurosciences and Rehabilitation* (2001 to 2006);
  - *Advances in Clinical Rehabilitation* (1987 to 1990);
  - *Archives of Occupational Therapy* (renamed *Occupational Therapy and Rehabilitation;* 1922 to 2006);
  - *Canadian Journal of Rehabilitation* (1987 to 1999);
  - *Chinese Journal of Physical Medicine and Rehabilitation* (1980 to 2006);
  - *European Journal of Physical Medicine and Rehabilitation* (1991 to 1999);
  - *International Journal of Rehabilitation and Health* (1995 to 2000);
  - *Journal of Rehabilitation Administration* (1987 to 2006);
  - *Rehabilitation* (1948 to 1949, 1951 to 1977);
  - *Rehabilitation in Canada* (1963 to 1972);
  - *Rehabilitation Nursing Research* (1992 to 1996);
  - *Topics in Stroke Rehabilitation* (1995 to 2006).
- We sought information about unpublished or incomplete trials via correspondence with researchers or organisations (or both), known to be involved in previous relevant studies.
- We checked the bibliographies of included studies and relevant reviews for further references to additional relevant trials.

Data collection and analysis

Selection of studies

We selected trials for inclusion based on the described inclusion criteria. For this update, one review author (PL) read all the references identified and eliminated any obviously irrelevant studies. Two review authors (selected from MT, JMC, PL, JB, TB) independently read the titles (and abstracts if available) of the identified references. We obtained the full text for remaining studies, and based on the inclusion criteria (types of studies, types of participants, aims of interventions, outcome measures), two review authors (selected from MT, JMC, PL, JB, TB) independently classified these as eligible, not eligible, or unsure. We excluded any trials that both review authors classified as not eligible. At least two review authors (selected from MT, JMC, PL, JB, TB) independently made decisions about inclusion, and we resolved differences in opinion regarding trial eligibility by discussion between all review authors. If further information was needed to reach consensus, we contacted trialists, and attempted to obtain the missing information. We arranged trial selection decisions to avoid trialists making decisions about trials in which they were involved.

Papers and abstracts in Chinese were reviewed by one researcher fluent in Chinese and with medical training (YL, JW, or WZ, *see* Acknowledgements). One review author (MT or PL) assessed a short English description of the decision made.

Data extraction and management

Our primary aim was to obtain standardized data through collaboration with the original trialists. Two review authors (from MT, JMC, PL, TB) independently extracted data from published sources, using a standard data recording form. We extracted important risk of bias indicator data such as concealment of randomization, blinding of outcome evaluation, and intention-to-treat analysis, and graded these as present, absent, or unclear. In addition, we extracted data relating to all primary and secondary outcomes of interest, as well as important imbalances in prognostic factors, comparison (details of the intervention in the treatment and control groups, details of co-intervention(s) in both groups), and other relevant outcomes not prespecified in the protocol (for example, exertion).

The review authors checked all the extracted data for agreement; a third review author arbitrated any items where they could not reach consensus. If necessary, we contacted trialists to request more information, clarification, or missing data.

Assessment of risk of bias in included studies

Two review authors (from PL, MT or TB), who had no involvement in the study under review, independently evaluated the risk of bias of included trials, using the Cochrane 'Risk of bias' tool, and extracted information for each included trial about the method of randomization and allocation concealment, blinding of outcome assessment, and any intention-to-treat analyses. We applied the GRADE approach to assess the quality of the evidence (Higgins 2011).

Measures of treatment effect

We compared interventions that commenced mobilisation earlier and aimed to improve the frequency or amount (or both) of mobilisation activity, delivered by any member of the acute stroke unit staff, versus more delayed mobilisation (usual care) on primary and secondary outcome measures. We analysed binary (dichotomous) outcomes with a fixed-effect model, as odd ratios (OR) with 95% confidence intervals (CI). For continuous outcomes, we calculated a mean difference (MD) with a random-effects model, to take account of any statistical heterogeneity. We used the standardized mean difference (SMD) where different scales were used for the same outcome.

Unit of analysis issues

We only included randomized parallel group trials, in which the unit of analysis was the individual participant. We did not include cluster- or cross-over RCTs.

Dealing with missing data

We assessed the degree of missing data for each of the main outcomes and had planned to conduct sensitivity analyses if more than 15% of randomized participant data were missing.

Assessment of heterogeneity

We examined the statistical heterogeneity between studies using the I^2 statistic. We determined substantial heterogeneity as a value greater than 50%.

Assessment of reporting biases

We had planned to carry out funnel plots if more that 10 trials were available.

Data synthesis

If continuous data were only available as medians and interquartile ranges, we estimated the mean using an established method (Wan 2014). Where only interquartile ranges (IQR) were reported, we inferred the standard deviation as follows: the IQR will incorporate 50% of the distribution of data compared with standard deviation, which can be expected to include 70% (± 35%) of the distribution. Therefore, assuming a normal distribution, one standard deviation should equal the IQR/(2 x 0.7). We used the Cochrane Review Manager 5 software for analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We did not plan subgroup analyses for this version of the review, which did not have individual patient data available. We planned to explore heterogeneity through sensitivity analyses.

Sensitivity analysis

We conducted sensitivity analyses to evaluate the effect of differences in methodological quality (method of randomization, allocation concealment, intention-to-treat analysis, and blinding of final assessment), time-to-first mobilisation, and amount of mobilisation activity.

Network meta-analysis

In view of new approaches to meta-analysis, we also included a post-hoc network meta-analysis (NMA) of trial data. This review aimed to include trials that compared the effect of a shorter time-to-first mobilisation (with or without an increase in the amount or frequency (or both) of mobilisation activities) with usual care (where time-to-first mobilisation started later). However, we expected that within this broad definition, the included trials would comprise a range of treatment comparisons. Therefore, we included an exploratory NMA to explore, where possible, the impact of

different treatment characteristics (time-to-first mobilisation and amount of mobilisation activity). We used Metainsight software, designed specifically for this role, to conduct our NMA (https://crsu.shinyapps.io/metainsightb/).

A NMA uses information from both direct and indirect estimates of treatment effect (Tonin 2017). Direct estimates are provided by a head-to-head comparison (e.g. treatment A versus treatment B). Indirect estimates are provided by two or more head-to-head comparisons that share a common comparator (e.g. when A verus B is the comparison of interest, then use trials with A versus C and with B versus C). A network is then formed, using a collection of trials that allow, through direct and indirect comparisons, calculation of the relative effects of all treatments versus each other (or versus a single comparator).

A key assumption in NMA is the transitivity (or similarity) assumption that concerns the validity of making indirect comparisons. This assumes that treatment effects are 'exchangeable' across the included trials and all treatments are 'jointly randomisable'. In other words, all treatment categories could feasibly be randomized in the same trial and those that are not treatment arms in any given trial are 'missing at random' (Lu 2006). This assumption cannot be formally tested statistically, and it must be judged through careful consideration of the trial settings and characteristics, treatment mechanisms, and participant demographics to investigate if any differences would be expected to modify relative treatment effects.

A second key assumption (known as the consistency assumption) assumes that it is feasible to make indirect comparisons between two treatments, and that the indirect evidence is consistent with the direct evidence, where such a comparison exists (Lu 2006). The consistency assumption is evaluated statistically by comparing the difference between the direct and the indirect estimate for each loop of evidence. Therefore, we examined for any important differences in numerical results between direct, indirect, and network results.

Assessing the quality of the evidence

NMA presents challenges when grading the quality of evidence. We used the approach of the GRADE group as follows (Puhan 2014).

- Present direct and indirect treatment estimates for each comparison of the evidence network.
- Rate the quality of each direct and indirect effect estimate (downgrading for risk of bias, inconsistency, indirectness, imprecision, and publication bias).
- Present the NMA estimate for each comparison of the evidence network.
- Rate the quality of each NMA effect estimate (as above).

RESULTS

Description of studies

Please see Characteristics of included studies, Characteristics of ongoing studies, Characteristics of studies awaiting classification and Characteristics of excluded studies.

Results of the search

The collated searches from this, and the previous version of the review, identified 21,395 titles (Bernhardt 2009; Figure 1). The original version of the review identified a total of 39 trials of interest by September 2007, 28 of which we excluded; 10 were ongoing or unclassified, and one was included (AVERT II 2008).

Figure 1. Study flow diagram

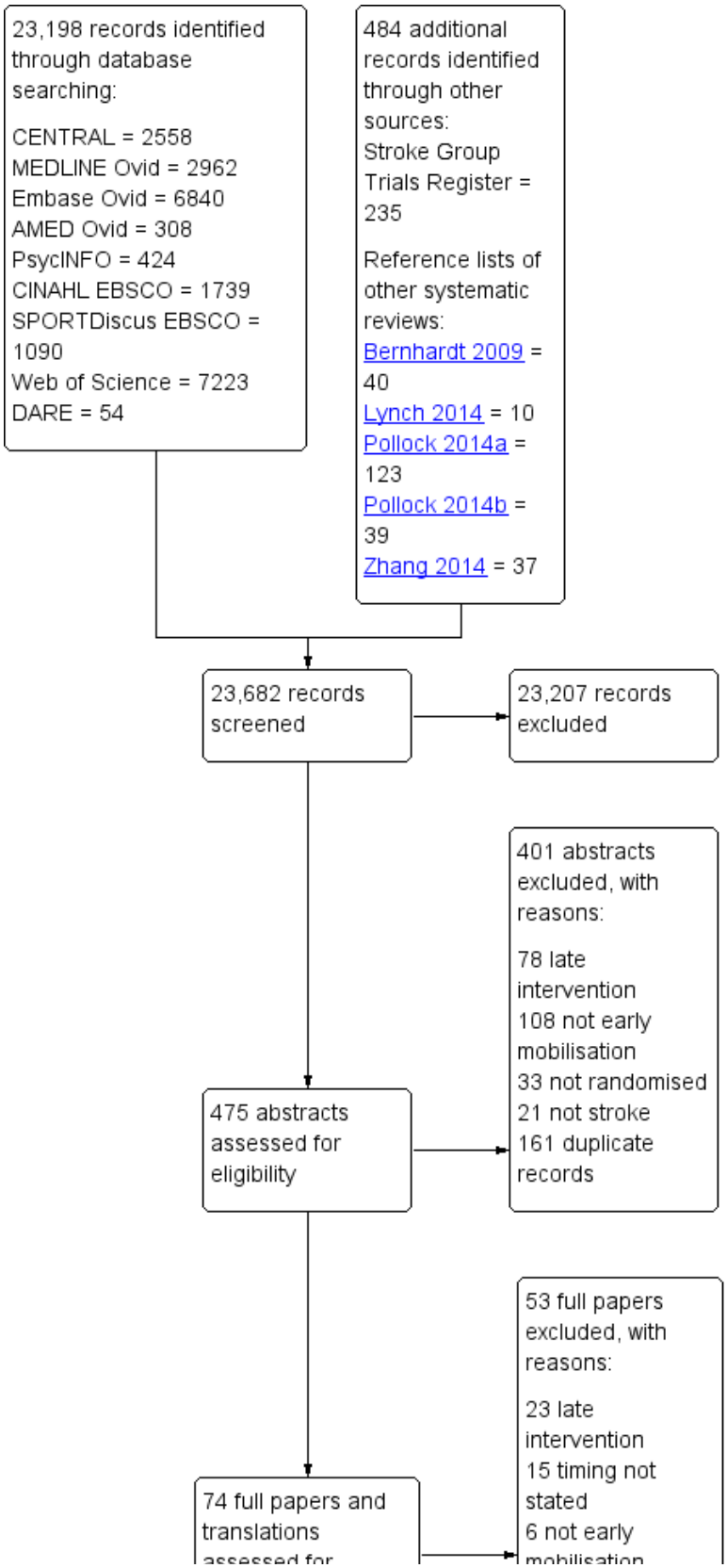
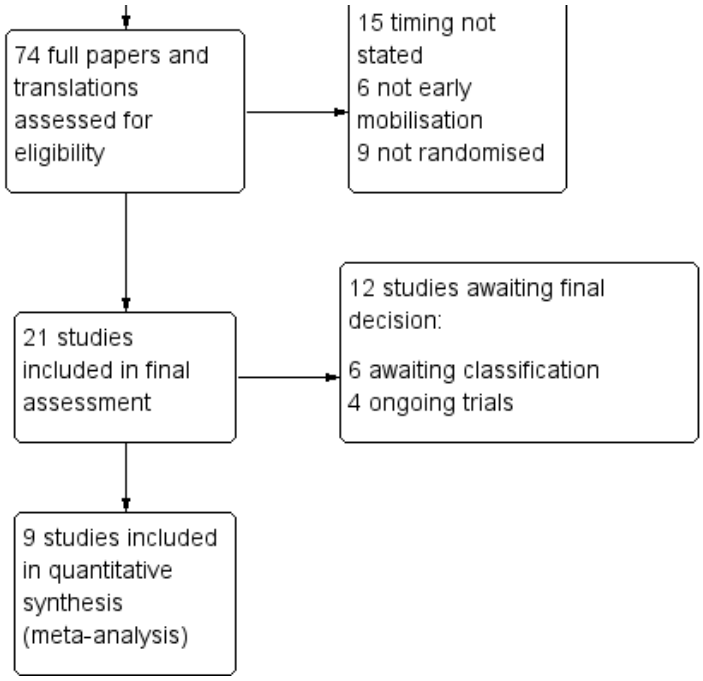


Figure 1. (Continued)



This update identified a total of 74 studies of interest, 53 of which we excluded for various reasons, as detailed in the 'Characteristics of excluded studies' table.

In addition to the excluded studies, there are eight studies for which we have been unable to obtain full references and for which we have been unsuccessful in obtaining any further information from the authors, therefore they are still awaiting classification (Izumi 2001; Liu 2010e; Nilsson 2003; Skevin 2009; Song 2010; Xu 2001; Zheng 2004a; Zielke 2003). Three trials are currently ongoing, with no available data (ChiCTR-ICR-15005992; ChiCTR-IPR-16008652; ChiCTR-TRC-08000201). They plan to recruit about 400 participants in total. One trial is in the development stage (AVERT-DOSE 2017). Details of these trials are reported in the 'Characteristics of ongoing studies' table.

Included studies

We included nine trials in the review (AVERT II 2008; AVERT III 2015; Chippala 2015a; Chippala 2015b; Langhorne 2010; Morreale 2016; Poletto 2015; SEVEL 2016; Sundseth 2012). Note that the 'Characteristics of included studies' table contains 11 items, because one trial contained two arms (Morreale 2016), which for some analyses had to be analysed separately (Morreale 2016 CTE; Morreale 2016 PNF).

The nine included trials had a total of 2958 participants; the inclusion and exclusion criteria are shown in the 'Characteristics of included studies' table. The included participants were broadly representative of the stroke population, although the numbers were dominated by one multicentre trial of 2104 participants (AVERT III 2015). Across all nine included trials, the mean age of participants within each trial ranged from 60 to 77 years (median 68), and the proportion of males ranged from 35% to 72% (median 52%). Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS), and usually classified as mild (NIHSS 0 to 7), moderate (NIHSS 8 to 16), or severe (NIHSS > 16) stroke (Brott 1989). The baseline stroke severity was typically in the moderate range, with the proportion with intracerebral haemorrhage ranging from 0% to 20% (median 12%).

We did not observe imbalances between groups in important prognostic factors, including age, stroke severity, type of stroke, and premorbid disability.

We categorised the intervention details using the TIDieR classification, which are summarized in the 'Characteristics of included studies' table (Hoffman 2014). The interventions were delivered in a stroke unit (AVERT II 2008; AVERT III 2015; Chippala 2015a; Chippala 2015b; Langhorne 2010; Poletto 2015; Sundseth 2012), stroke centre (SEVEL 2016), or neurology ward (Morreale 2016). The very early mobilisation (VEM) intervention was provided by physiotherapy, with or without nursing staff, and continued while the participant was in hospital. The nine trials all tested different versions of a VEM strategy as follows.

Earlier onset

In six trials, intervention participants were mobilised within 24 hours of stroke (AVERT II 2008; AVERT III 2015; Chippala 2015a; Chippala 2015b; Morreale 2016; Sundseth 2012), while in three, this usually occurred at 24 to 48 hours (Langhorne 2010; Poletto 2015; SEVEL 2016). Across all trials, the median (range) delay to starting mobilisation after stroke was 18.5 (13.1 to 43) hours in the VEM group, and 33.3 (22.5 to 71.5) hours in the usual care group. The median difference (range) within trials was 12.7 (4 to 45.6) hours.

More intensive

In four trials, VEM included a recorded increase in time of out-of-bed mobility activities (AVERT II 2008; AVERT III 2015; Langhorne 2010; Poletto 2015). One trial reported a longer time participants were recorded sitting out of bed, but not a very active mobilisation activity (SEVEL 2016). One trial reported a similar intensity (Sundseth 2012), but information was more limited from three others (Chippala 2015a; Chippala 2015b; Morreale 2016).

Modifiable intervention

Five trials reported that the intervention could be modified or stopped in the event of a deterioration in the participant's physiological or neurological status (AVERT II 2008; AVERT III 2015; Langhorne 2010; SEVEL 2016; Sundseth 2012). Information was more limited from four others (Chippala 2015a; Chippala 2015b; Morreale 2016; Poletto 2015).

Monitored intervention

In several trials, the difference in care delivered was timed and recorded. Five trials recorded an earlier onset of mobilisation with an increased number of minutes of out-of-bed activity (AVERT II 2008; AVERT III 2015; Langhorne 2010; Poletto 2015; SEVEL 2016). Three trials recorded an earlier onset of mobilisation, but no reported difference in activity (Chippala 2015a; Chippala 2015b; Sundseth 2012). We had limited information from one other trial (Morreale 2016).

Excluded studies

We excluded a total of 53 studies (AMOBES 2017; Asberg 1989; Chu 2003; Di Lauro 2003; Diserens 2010; Duan 2006; Fang 2001a; Fang 2001b; Gong 2003; Gorbunov 2003; Gu 2006; Guan 2001; Hamrin 1982; Hara 2001; Huang 2001; Huang 2003; Ishida 2001; Kreisel 2005; Li 1999; Li 2003; Li 2004; Lin 2005; Liu 2001b;Liu 2003b; Liu 2004; Marshall 2011; Miskovic 2004; Pan 2004; Qian 2003;Qian 2004; Raicevic 2000; Richards 1993; Sankara Kumaran 2013; Song 2005; Sun 2002; Toyota 2001; Truscott 1974; Wang 2004; Wang 2005; Wang 2006; Wu 2012; Xi 2003; Xiao 2000; Xiao 2004; Xie 2003a; Xue 2004; Xue 2006; Xue 2008; Zeng 2004; Zhang 1998; Zhang 2001; Zhao 2003; Zheng 2004; Zheng 2004a; Zielke 2003). Many of these studies were published in Chinese language journals and required translation to English. We excluded these trials for various reasons, as detailed in the 'Characteristics of excluded studies' table. The main reasons for exclusion were late intervention, not early mobilisation intervention, timing not stated, and not randomized.

Risk of bias in included studies

The risk of bias assessments are summarized in the Characteristics of included studies, and in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

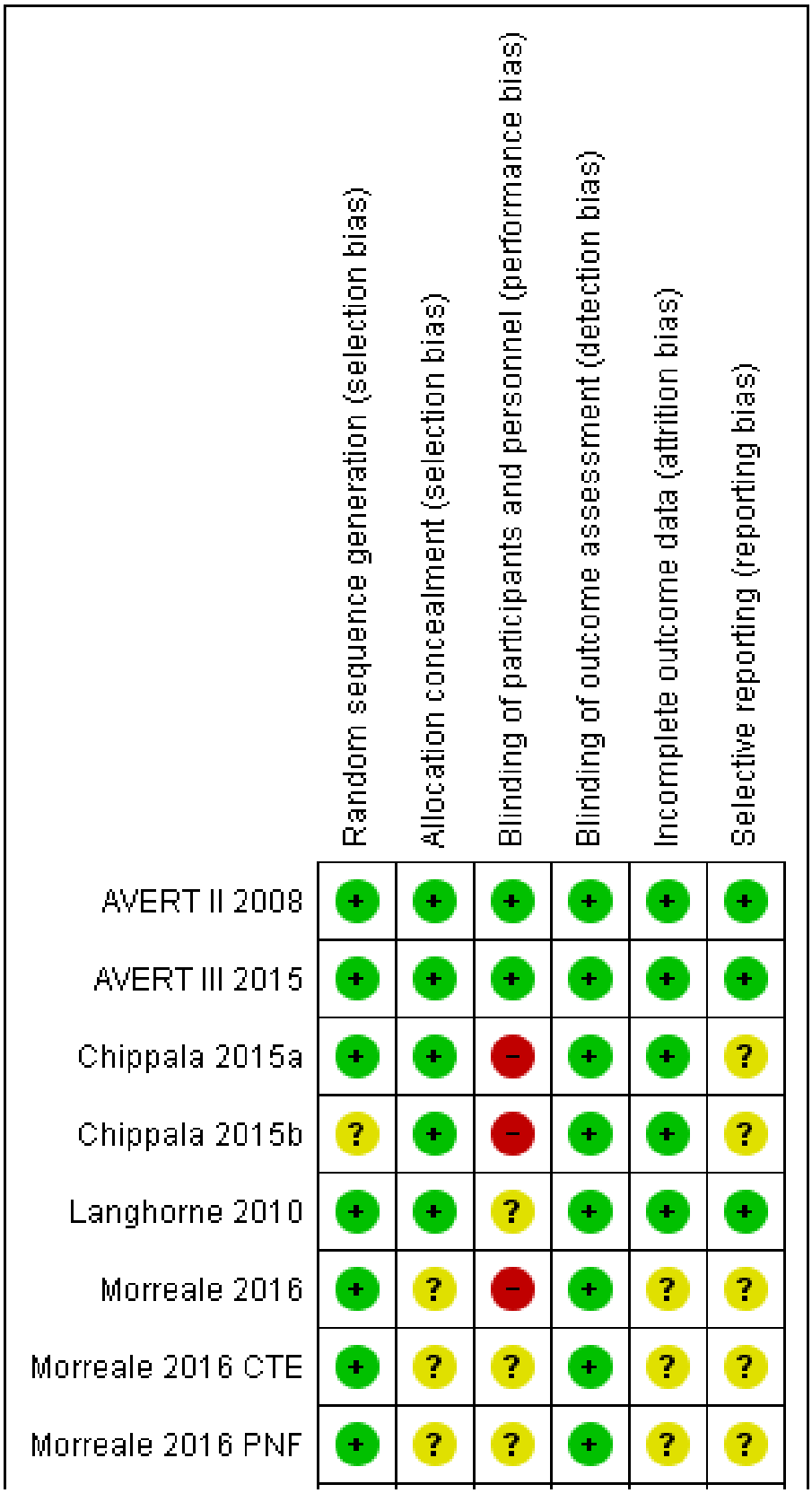


Figure 2. (Continued)

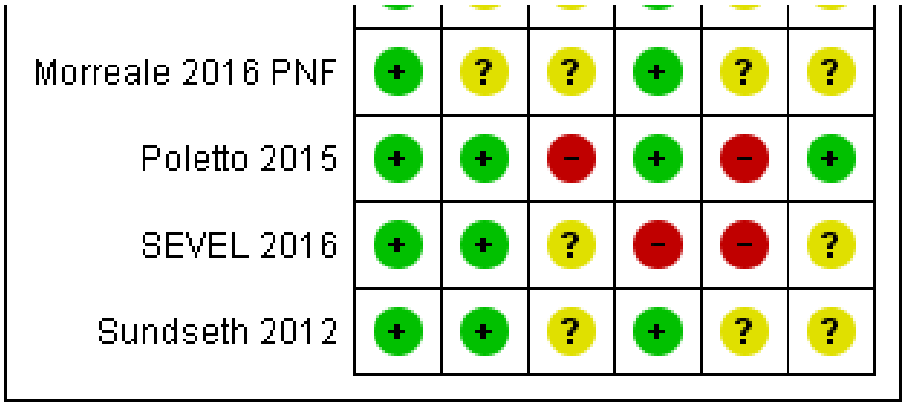
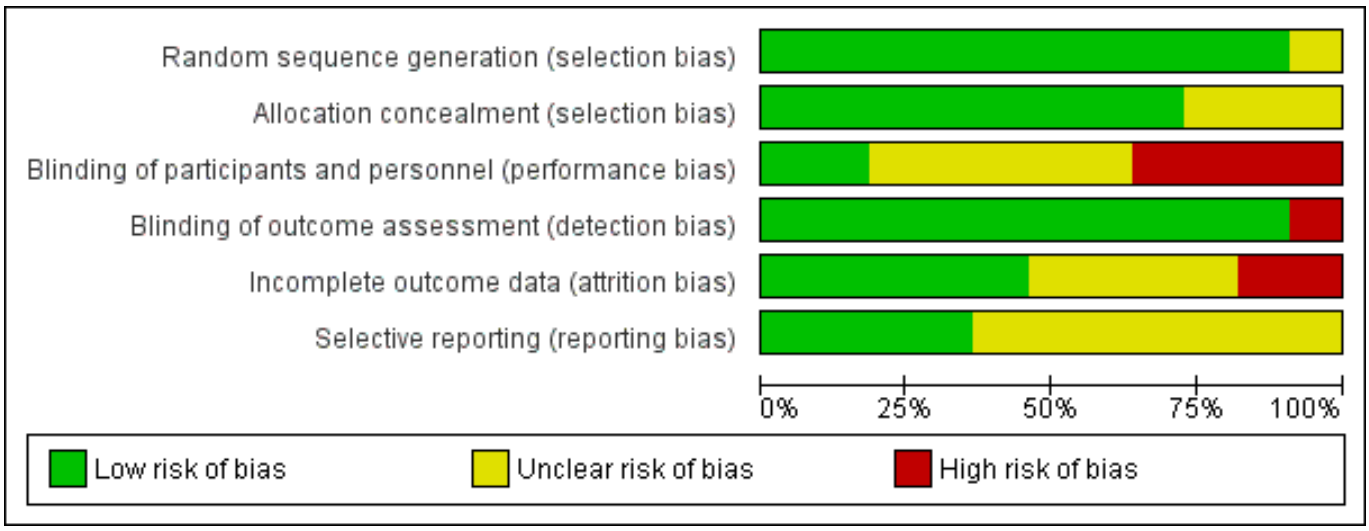


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

All trials reported using a computer-generated randomization schedule. Allocation was concealed by using sequential, opaque envelopes, or a secure, centralised randomization procedure.

We assessed random sequence generation to be at low risk of bias for eight studies, and unclear for one study (Chippala 2015b).

We assessed allocation concealment to be at low risk of bias for eight studies, and unclear for one study (Morreale 2016).

Blinding

Blinding of treating therapists and patients was challenging. In three trials, the treating staff were aware of the VEM protocol, but this was masked from the rest of the staff (AVERT II 2008; AVERT III 2015; Langhorne 2010). Patients were aware they were in a trial of different protocols, but the details were not emphasised. Blinding was uncertain for the other trials. We assessed blinding to be at low risk of bias for two studies (AVERT II 2008; AVERT III 2015), at unclear risk for three studies (Langhorne 2010; SEVEL 2016; Sundseth 2012), and at high risk for four studies (Chippala 2015a; Chippala 2015b; Morreale 2016; Poletto 2015).

All but one trial used an independent (blinded) assessor for the follow up of the primary outcome (SEVEL 2016). The security of blinding was less complete for secondary outcomes, such as in hospital complications.

Incomplete outcome data

Intention-to-treat analyses were not possible with incomplete outcome data. Therefore incomplete data were described for each outcome analysis. We assessed the risk of bias to be low in five studies (AVERT II 2008; AVERT III 2015; Chippala 2015a; Chippala 2015b; Langhorne 2010); unclear in two studies (Morreale 2016; Sundseth 2012); and high in two studies (Poletto 2015; SEVEL 2016).

Selective reporting

Reporting was largely complete for the primary outcome; nine trials included the primary outcome of death or dependence (mRS score 3 to 5) at three months post stroke, although one did not report this as dichotomous data (Morreale 2016). Data were available for 2542 of 2618 (97.1%) participants randomized, and followed up for a median of three months. In addition, three trials also planned or conducted follow-up at one year (AVERT II 2008; AVERT III 2015; Morreale 2016).

Data were less complete for the secondary outcome measures, which were usually conducted at three months. This was probably due to missing data (rather than selective reporting) when participants had to actively complete a score. These outcomes included: ADL score, extended ADL score, subjective health status, mood score, mobility, place of residence, presence and type of complications. Complications were usually recorded during the period of hospitalisation, and were divided into: 1) complications of immobility (chest infection, urinary infection, pulmonary thromboembolism, pressure sores), plus 2) others. Specific comments were made for each outcome listed in the 'Summary of findings' table (Summary of findings for the main comparison).

We do not presently have sufficient data for the planned subdivision of other complications into neurological causes (recurrent stroke, seizure, progressing stroke - defined according to the European Progressing Stroke Study definition (Barber 2004), or a progressive deterioration in the Scandinavian Stroke Scale or National Institutes of Health Stroke Scale).

Other potential sources of bias

Several of the review authors are trialists in this area and have publications included in this review. However, we arranged trial selection decisions to avoid trialists making decisions about their own trials.

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcome

Death or a poor outcome

Data were available from all trials, except Morreale 2016, for the outcome of death or a poor outcome, at the end of scheduled follow-up. Within these eight trials, data were available for 2542 of 2618 participants randomized (97.1%). The number of participants dying or having a poor outcome at the end of scheduled follow-up was similar in those who received VEM (640/1262, 50.7%) to those in the usual care group (622/1280, 48.6%; odds ratio (OR) 1.08, 95% confidence interval (CI) 0.92 to 1.26; P = 0.36; Analysis 1.1; moderate-quality evidence)). There was substantial heterogeneity (68%); reanalysis with a random-effects model did not alter the conclusions (fixed effect OR 1.08, 95% CI 0.92 to 1.26; random effects OR 0.77, 95% CI 0.45 to 1.31).

Analysis using outcomes collected at three-month follow-up did not alter the conclusions. It is notable that the original pre-planned analysis of the largest trial, which contributed 2104 of the total of 2618 (80%) participants included, found increased odds of death or poor outcome (mRS 3 to 6) at three months, after adjustment for prognostic factors (adjusted OR 1.37, 95% CI 1.11 to 1.69; P = 0.004; unadjusted OR 1.17, 95% CI 0.99 to 1.39; P = 0·06; Analysis 2.1; AVERT III 2015).

Secondary outcomes

Death

Data were available from all trials, except Morreale 2016, for the outcome of death, at the end of scheduled follow-up. Within these eight trials, data were available for 2561 of 2618 participants randomized (97.8%). There was no statistically significant difference in the number of deaths at the end of scheduled follow-up among those who received VEM (108/1274, 8.5%) compared with the control group (87/1287, 6.8%; OR 1.27, 95% CI 0.95 to 1.70; P = 0.11; Analysis 1.2; moderate-quality evidence). There was little heterogeneity (0%). Analysis using outcomes collected at three-month follow-up did not alter the conclusions (Analysis 2.2).

Death or dependence

Data were available from all trials, except Morreale 2016, for the outcome of death or dependence (mRS 3 to 6), at the end of scheduled follow-up. Within these eight trials, data were available for 2542 of 2618 participants randomized (97.1%). There was no clear difference in the risk of participants dying or remaining dependent in those who received VEM (640/1262, 50.7%) compared with the control group (622/1280, 48.6%) at the end of scheduled follow-up (OR 1.08, 95% CI 0.92 to 1.26, P = 0.36; Analysis 1.3; moderate-quality evidence). There was substantial heterogeneity (68%). Re-analysis with a random-effects model did not alter the conclusions. Analysis using outcomes collected at three-month follow-up did not alter the conclusions (Analysis 2.3).

Please note that because we had access to our preferred dependence data for the primary (poor) outcome (Analysis 1.1 and Analysis 2.1), the death or dependence outcomes (Analysis 1.3 and Analysis 2.3) were identical to the primary outcome.

Death or institutional care at end of scheduled follow-up

Data were available from only three trials for the outcome of death or requiring institutional care, at the end of scheduled follow-up (AVERT II 2008; Langhorne 2010; SEVEL 2016). Overall data were available for only 227 of 270 participants randomized (84.1%). There was no clear difference in the risk of participants dying or requiring institutional care at the end of scheduled follow-up in those who received VEM (21/112, 18.8%) compared with the control group (20/115, 17.4%; OR 1.05, 95% CI 0.53 to 2.07, P = 0.89; Analysis 1.4). There was little heterogeneity (20%). Analysis using outcomes collected at three-month follow-up did not alter the conclusions (Analysis 2.4).

Performance in activities of daily living

Data were available from all trials, except Chippala 2015b, for the outcome of activities of daily living (ADL) score, at the end of scheduled follow-up. All trials used the Barthel Index, so we converted scores to a standard scale of 0 to 20. Overall, data were available for 2630 of 2909 participants randomized (90.6%). There was a higher mean ADL score for those who received VEM, compared with the control group (mean difference (MD) 1.94, 95% CI 0.75 to 3.13; P = 0.001; Analysis 1.5; low-quality evidence). There was substantial heterogeneity (93%), so we completed the analysis using a random-effects model. Cautious interpretation is also required, because the Barthel Index often has a non-normal distribution.

Most trials included terminal follow-up at three months, so many of the data are the same in both analyses. Analysis using outcomes collected at three-month follow-up resulted in a smaller observed effect size (MD 0.75, 95% CI 0.01 to 1.49; P = 0.05; Analysis 2.5); low-quality evidence) and a lesser degree, although still substantial, of heterogeneity (80%), so we used a random-effects model for analysis.

Performance in extended activities of daily living (community and domestic activities)

No data were available for this outcome.

Patient subjective health status and quality of life

Only AVERT II 2008 reported this outcome in the form of the Assessment of Quality of Life scale. They found no significant difference between groups (MD 0.07, 95% CI -0.10 to 0.23; P = 0.42; 1 trial, 68 participants; Analysis 1.6; very low-quality evidence).

Able to walk and mobility score

Data were available from four trials for the outcome of being able to walk at follow-up (AVERT II 2008; AVERT III 2015; Langhorne 2010; Sundseth 2012). Within these four trials, data were available for 2255 of 2272 participants randomized (99.3%). There was no clear difference in the number of participants able to walk among those who received VEM (831/1130, 73.5%) compared with the control group (827/1125, 73.5%) at follow-up (OR 1.00, 95% CI 0.83 to 1.21; P = 0.99; Analysis 1.7). There was substantial heterogeneity (60%), but re-analysis with a random-effects model did not alter the conclusions.

Data were available from only two trials for the outcome of mobility score at the end of scheduled follow-up (AVERT II 2008; Langhorne 2010). Within these two trials, data were available for 102 of 103 participants randomized (99.0%). There was no significant difference in the mean score between those who received VEM compared with the control group (standardized mean difference (SMD) 0.14, 95% CI -0.27 to 0.56; P = 0.50; Analysis 1.8). There was no substantial heterogeneity (8%).

Complications: any complication

Data were available from all trials, except Chippala 2015a, Chippala 2015b, and SEVEL 2016, for the outcome of participants who reported any complication, recorded at follow-up. Within these six trials, data were available for 2778 of 2818 participants randomized (98.6%). There was no statistically significant difference in the risk of participants developing a complication among those who received VEM (287/1436, 20.0%) compared with the control group (301/1342, 22.4%) at the end of scheduled follow-up (OR 0.88, 95% CI 0.73 to 1.06; P = 0.18; Analysis 1.9; low-quality evidence). There was no substantial heterogeneity (0%).

When complications were divided into those classified as complications of immobility and other complications, there was no significant difference between groups (test for subgroup differences P = 0.23; Analysis 1.10). We had insufficient information to analyze by severity of complication, or other types of complication.

Patient mood at the end of scheduled follow-up

Only two trials reported this outcome (AVERT II 2008; Sundseth 2012). There was no significant difference between groups (SMD 0.07, 95% CI -0.33 to 0.46; P = 0.74; 2 trials, 100 participants; Analysis 1.11).

Length of stay in acute hospital

Data were available from all trials, except Morreale 2016, for the outcome of length of acute stay in hospital. Within these eight trials, data were available for 2551 of 2618 participants randomized (97.4%). Seven of the eight trials reported a shorter length of stay in the VEM group. Across all trials, there was a shorter mean length of stay for the group who received VEM compared with the usual care group (MD -1.44, 95% CI -2.28 to -0.60; P = 0.0008; Analysis 1.12; low-quality evidence). There was no substantial heterogeneity (26%), but we completed the analysis using a random-effects model, because of the variable definitions of length of stay. This result was largely driven by two small trials, with narrow standard deviation values (Chippala 2015a; Chippala 2015b). Cautious interpretation is also required because the length of stay often has a non-normal distribution.

Sensitivity analysis

Trial quality: none of the outcome conclusions were altered if we restricted analysis to trials with the highest methodological quality (based on method of randomization, allocation concealment, completeness of follow-up, and blinding of final assessment), or information about the amount of mobilisation.

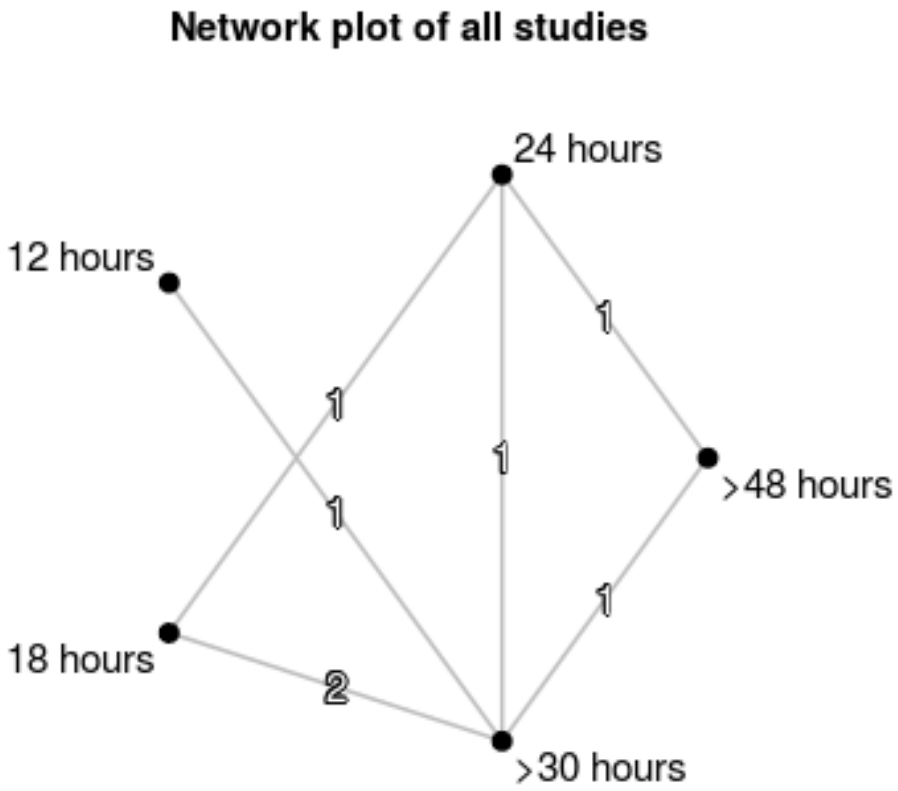
Intervention features: sensitivity analyses restricted to trials with an earlier time-to-first mobilisation (mean time-to-first mobilisation of less than 24 hours) showed a similar primary outcome to the main analysis (OR 1.10, 95% CI 0.93 to 1.29; P = 0.27; I^2 = 78%), and an odds of death of 1.35 (95% CI 0.99 to 1.83; P = 0.06; I^2 = 25%; AVERT II 2008; AVERT III 2015; Chippala 2015a; Chippala 2015b; Sundseth 2012). Analyses restricted to the trials that clearly recorded a more prolonged out-of-bed activity, showed a similar primary outcome (OR 1.14, 95% CI 0.96 to 1.35; P = 0.13; I^2 = 28%), and odds of death (OR 1.27, 95% CI 0.93 to 1.73; P = 0.13; I^2 = 0%) to the main analysis (AVERT II 2008; AVERT III 2015; Langhorne 2010; Poletto 2015).

Network meta-analysis (NMA)

This review included trials that aimed to compare the effect of reducing time-to-first mobilisation (TTFM), with or without an increase in the amount or frequency of mobilisation activities, with usual care (where TTFM started later). However, it was clear that within this definition, the included trials would comprise a range of different comparisons. Therefore, we conducted an exploratory, post-hoc, network meta-analysis (NMA) to explore, where possible, the impact of treatment characteristics (TTFM and amount of mobilisation activity). NMA analysis by the amount of mobilisation activity was not possible, because this information was not consistently reported (Table 1). However, we could categorise information on TTFM into five major TTFM groups, with limited overlap.

Table 2 shows the categories of TTFM, with early mobilisation TTFM in the columns, and usual care TTFM in the rows. The lower left section indicates the trials (participants) contributing to each direct comparison of TTFM. Figure 4 shows the same comparisons in the form of a network plot.

Figure 4. Network plot of all trials. Each point shows the time-to-first mobilisation (TTFM) classifications. The lines show the number of trials directly comparing each TTFM category.



We believe that the transitivity (or similarity) assumption was met, as all the included trials recruited people with acute stroke, within 48 hours of symptom onset, within a stroke unit (or similar) setting. The IQR distribution for average age (65 to 73 years), gender (45% to 57% male), and stroke severity (44% to 68% moderate or severe) were broadly comparable (Table 1).

We evaluated the consistency assumption statistically, by comparing the difference between the direct and the indirect estimate for each loop of evidence. We examined for any inconsistency (i.e. important differences in numerical results between direct, indirect, and network results), and we presented OR estimates for each of the three comparisons.

We showed the inconsistency tables for the NMA for the analyses of poor outcome (Table 3), and death (Table 4). These tables show the results of direct and indirect comparisons, plus the NMA results. There were no statistically significant differences between any of the direct and indirect comparisons, but the confidence intervals were wide (Table 5).

The NMA used the 24-hour TTFM group as the comparator, as this was clinically relevant and incorporated the largest single trial (AVERT III 2015). Figure 5 shows the NMA result for the poor outcome (death or dependency) at three months. The lowest odds of poor outcome was at 24 hours, although confidence intervals were very wide. A similar pattern was seen for the outcome of death at three months (Figure 6), but again with very wide confidence intervals (Table 5).

Figure 5. Network meta-analysis plot for poor outcome (death or dependency at 3 months). The treatment column shows the time-to-first mobilisation (TTFM) categories. The results are the odds ratio (95% confidence interval) for the odds of a poor outcome with TTFM of 24 hours as the reference (OR = 1.0).

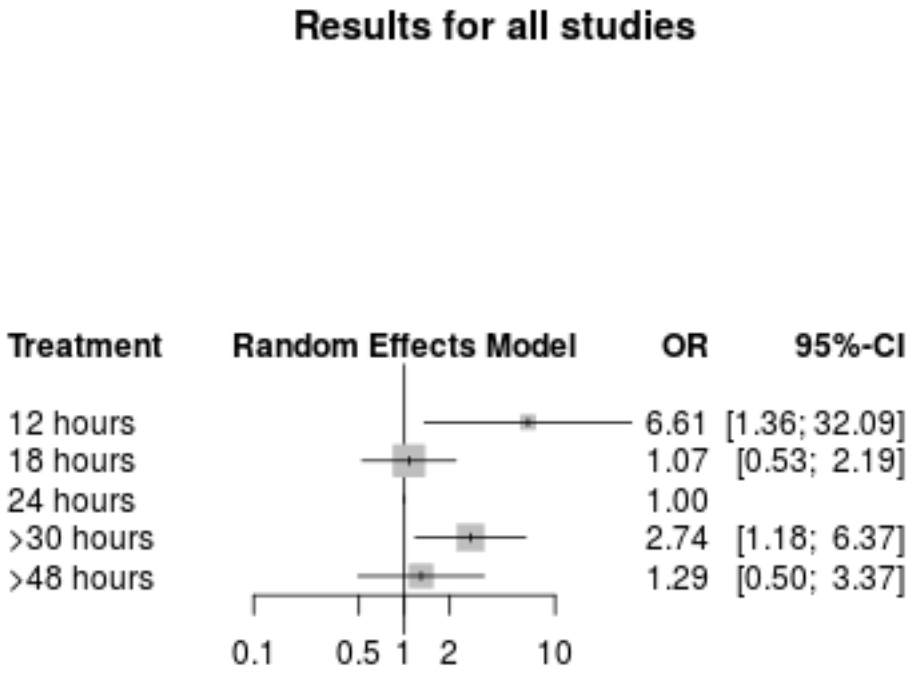
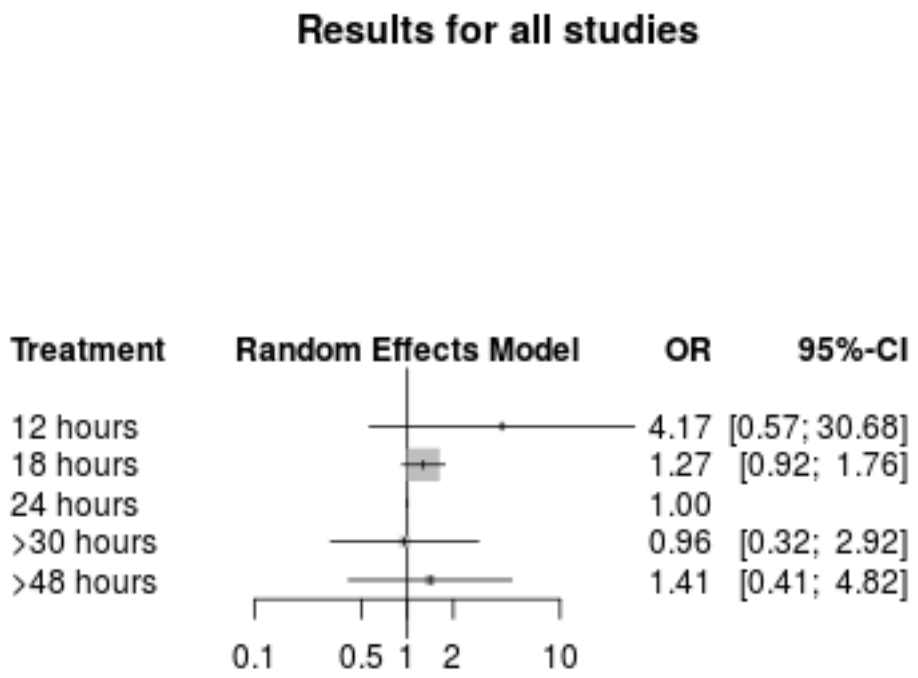


Figure 6. Network meta-analysis plot for death at 3 months. The treatment column shows the time-to-first mobilisation (TTFM) categories. The results are the odds ratio (95% confidence interval) for the odds of death with TTFM of 24 hours as the reference (OR = 1.0).



Finally, we carried out a Rank analysis, which orders treatments according to their relative effectiveness; the first ranked treatment is most likely to be the most effective treatment, compared with the other treatments in the network. This analysis rated the 24-hour TTFM group to be the one most likely to be associated with efficacy (P = 0.81 for poor outcome), and safety (P = 0.76 for death by three months), indicating that 24-hour TTFM was the optimal option, although our confidence was limited by the substantial imprecision.

DISCUSSION

This systematic review aimed to assess the benefits or harms of very early mobilisation (VEM) compared with conventional practice (usual care). We conducted a comprehensive search of citation and clinical trial registries, and contacted researchers in the field to identify unpublished studies. We identified 13 eligible RCTs, nine (2958 participants) of which we included: three from China are currently underway or not yet published, and one is in the planning stage (AVERT-DOSE 2017).

Summary of main results

The included trials incorporated different approaches to VEM, but all included an earlier onset of out-of-bed mobilisation, and several reported providing a higher intensity (minutes per day) of mobilisation activity. The primary outcome (death or poor outcome) was not significantly altered by the mobilisation strategy. Neither were the other major binary outcomes: death, death or dependency, death or requiring institutional care, presence of complications, or ability to walk. We assessed the evidence for these outcomes as being of moderate quality. There was an indication that VEM may result in a higher ADL score among survivors, and a slightly shorter length of hospital stay. However, these conclusions were based on less reliable data that may have non-normal distributions, and are more prone to bias (low-quality evidence). Sensitivity analyses raised the possibility that trials with an earlier onset of VEM may have had a higher risk of death at the end of follow-up.

The review was dominated by one large, multicentred trial, involving 2104 participants from six countries (AVERT III 2015). The results

of AVERT III 2015 suggested a hazard with VEM (adjusted odds ratio (OR) for death or dependency at three months was 1.37, 95% confidence interval (CI) 1.11 to 1.69; P = 0.004). Pre-specified dose-response analyses suggested that better outcomes were associated with more frequent, and less prolonged episodes of mobilisation (AVERT III 2015).

Overall completeness and applicability of evidence

Clearly, there is considerable research interest in this field; we identified a number of recent trials. Despite this significant body of potentially relevant research, very few studies met the inclusion criteria. One of the major problems we identified during our search for relevant research, was that the term 'early rehabilitation' was used to define interventions spanning a wide time interval. For example, some authors used the term 'early' to describe an intervention that commenced within 48 hours post stroke (Xue 2004), while other authors described interventions commencing within three months of stroke as 'early' interventions (Li 2002). It is likely that what clinicians and researchers consider as early rehabilitation is strongly dependent on when rehabilitation usually commences within their healthcare system, and that this varies considerably between countries.

The most common reason we excluded trials from this review was that the mobilisation interventions in the experimental group commenced more than 48 hours after stroke symptom onset. Also, a few studies failed to detail the time from stroke onset, instead noting time from admission (e.g. Asberg 1989; Gao 2001). Given that it can take patients hours or even days to reach hospital following a stroke, these studies failed to provide a precise time point from stroke onset to commencing intervention, and consequently, we could not include the trials. Other studies provided insufficient information about the timing of the intervention to allow confirmation that the trial met the inclusion criteria. We attempted to contact study authors, and we are awaiting responses. Poor definition of the intervention content and dose was also a problem in this review. It was not uncommon to find interventions only broadly defined, with limited information about how much mobilisation was delivered by whom, how often, and over what time frame (days or weeks). Once again, we attempted to contact the study authors to seek further information.

Despite the uncertainties within the research field, our included trials, in particular AVERT III 2015, appeared to have included a representative patient population of those who are receiving cared in routine stroke unit settings. These trials generally took a pragmatic approach, and recruited a reasonably representative population in terms of age, sex, stroke type, and stroke severity. The data completeness for the key binary outcomes was generally good, but less secure for the continuous outcomes.

We planned the analysis of treatment characteristics in the expectation that within our broad comparison of early versus later onset mobilisation, the included trials would comprise a range of treatment comparisons. Therefore, we included an exploratory post-hoc network meta-analysis (NMA) to explore the impact of treatment characteristics (time-to-first mobilisation, and amount of mobilisation activity). We were unable to conduct NMA analysis by the amount of mobilisation activity because this information was not consistently reported between trials. However, we could categorise information on time-to-first mobilisation (TTFM) into five major TTFM groups with limited overlap. This analysis suggested that for both death and poor outcome (death or dependency) at three months, the optimal TTFM was about 24 hours. However, considerable caution is required in interpreting this result. First, this was an exploratory post-hoc analysis. Second, the TTFM categories were not absolutely discrete groups; we imposed the classification to fit the available trials. Third, the trials differed in type and quantity of mobilisation activity as well as TTFM. As a result, the confidence intervals were wide, and we graded the quality of the evidence as low. Therefore, we could conclude that further trials were warranted, but the limited information available at present did not indicate that any TTFM was superior to 24 hours (IQR 22 to 29).

Quality of the evidence

The nine trials included in the review showed a low risk of selection bias and were largely secure against detection bias (Figure 2). The most challenging aspect was the blinding of staff and participants. For some rehabilitation interventions, such as VEM, it may not be possible to have a truly double-blinded study; however, several trials attempted to mitigate such potential sources of bias (AVERT II 2008; AVERT III 2015; Langhorne 2010; Morreale 2016). First, participants were informed that they could be randomized to one of two styles of rehabilitation (AVERT II 2008), or treatment protocols (AVERT III 2015; Langhorne 2010), but the details of these protocols were not usually explained in detail. Second, the intervention was not made available to personnel beyond the treating staff, and efforts were made to avoid contamination (e.g. by providing treatment behind curtains (AVERT II 2008; AVERT III 2015; Langhorne 2010; Morreale 2016)).

Potential biases in the review process

Several of the review authors (JB, PL, JC, AS) were trialists in at least one of the included trials. However, we ensured that trial selection decisions were allocated in a manner that avoiding trialists making decisions about their own trials.

Our review identified a substantial number of trials from China that addressed the topic of early rehabilitation following stroke. We understand that current usual practice in many places in China, is to provide little or no organised rehabilitation to people following stroke. Therefore, it was likely that these trials, many of which were undertaken over the past 10 years, reflected an increased interest in the provision of rehabilitation to people with stroke. Unfortunately, none of Chinese trials we identified in this review met the inclusion criteria, because they provided either a complete multidisciplinary rehabilitation program or package, which may or may not have included a mobilisation component, and compared this with no rehabilitation (e.g. Xue 2004; Liu 2010e), or did not provide details of the time of commencement of mobilisation (e.g. Zhang 1998). In view of this rapidly growing body of Chinese research and the difficulties associated with acquisition and translation of Chinese research, it would be beneficial to form partnerships with Chinese researchers on the topic of early rehabilitation (Zhang 2014).

The analyses of continuous outcomes reported in this review were all subject to potential bias, and we rated them as providing low-quality evidence (Summary of findings for the main comparison). Although the main measure of activities of daily living (the Barthel ADL index) is a 20-point ordinal scale, its characteristics in people with stroke approximate to that of a continuous scale, and analysis using mean and standard deviation is usually justifiable (Song 2006). However, we downgraded the ADL data, because there was

a high level of statistical heterogeneity, and a substantial rate of missing data (for instance, participants who died were not included). Analysis of length of stay was confounded by the variable definitions of length of stay, and the likelihood that these data may be non-normally distributed. For both outcomes, re-analysis of individual patient data would provide a more reliable estimate of effect.

The network meta-analysis was exploratory in nature and had a number of uncertainties. Therefore, we judged the evidence for these conclusions to be low quality (Table 5).

Agreements and disagreements with other studies or reviews

This review update appeared to add substantive information to this field. Recent reviews published in this area identified fewer new RCTs, and concluded that the benefits of commencing physical rehabilitation within 24 hours of stroke were unclear. Lynch 2014 identified three new RCTs, and Bernhardt 2015 identified four RCTs, and concluded that the evidence was inconclusive. Whaley 2016 included two trials, and concluded that evidence supported a rested approach to care within the first 24 hours of hospitalisation. Finally, a recent review with different inclusion criteria concluded that there were no beneficial effects from VEM (Xu 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The approach to very early mobilisation (VEM) described in the trials we reviewed always featured an earlier onset of out-of-bed mobilisation activities, and often reported providing a higher intensity (time per day) of mobilisation activity. Overall, there was no significant impact of VEM on the main clinical outcomes (death, dependency, institutional care, presence of complications, ability to walk), although the largest single trial, AVERT III 2015, found a significant increase in death or dependency. We based our suggestions that VEM may result in a higher ADL score among survivors and a slightly shorter length of hospital stay on less reliable data that were more prone to bias.

We believe that the evidence supported a cautious approach to active mobilisation within 24 hours of stroke onset because the single largest trial (AVERT III 2015), and a sensitivity analysis of trials recruiting within 24 hours, raised the possibility that VEM commencing within 24 hours may carry some increased hazard. In addition, low-quality evidence from an exploratory network meta-analysis indicated that mobilisation at around 24 hours may be associated with the best outcome.

Implications for research

Larger, high-quality trials of VEM are needed to clarify the relative harms and benefits of different mobilisation strategies. In particular, these studies need to clearly define the optimal timing of commencement, frequency, and duration of mobilisation interventions. Timing should be provided from time of stroke symptom onset, not admission. Researchers must ensure publications fulfil CONSORT guidelines, with adequate description of the experimental and control interventions (Moher 2001).

We recommend that researchers and clinicians move to using a common terminology, as outlined in recent recommendations to improve the development and reporting of rehabilitation trials (Bernhardt 2017). We have proposed the term 'very early' rehabilitation to indicate interventions commencing within two days, and 'early' as those commencing three to seven days following stroke onset (Bernhardt 2007). In this time-critical field of research, it is also important that researchers clearly define when interventions commenced (hours), and that the time is estimated from the start of stroke symptom onset. Interventions should be described in a standard manner, such as with the TIDieR framework (Hoffman 2014). In the interim, an individual patient data meta-analysis of the existing trials may help explore some of the current uncertainties.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AVERT II 2008

Methods	RCT of very early and intensive mobilisation versus standard care Computer-generated blocked randomization, stratified by stroke severity and clinical site, opaque envelopes Blinded outcome assessment, participants blind to group

AVERT II 2008 *(Continued)*

Participants	Stroke units in 2 large teaching hospitals in Melbourne, Australia 71 participants: 38 intervention, 33 control Mean age: 74.7 years 53.5% male 9 (13%) haemorrhagic stroke Mean NIHSS 10 30 (42%) had mild stroke (NIHSS 1 to 7) 24 (33%) moderate stroke (NIHSS 8 to 16) 17 (24%) severe stroke (NIHSS > 16) Inclusion criteria: acute stroke patients admitted within 24 hours of symptom onset to a stroke unit, able to react to verbal commands, systolic BP 120 to 220 mmHg, oxygen saturation > 92% (with or without supplementation), heart rate 40 to 100, temperature < 38.5 C Exclusion criteria: premorbid mRS > 2, deterioration within first hour of admission to stroke unit, direct admission to intensive care, concurrent progressive neurological disorder, acute coronary syndrome, severe heart failure, lower limb fracture, palliative care
Interventions	**What** Procedures: VEM plus standard care versus standard care alone. The VEM group commenced mobilisation (upright and out of bed at least twice a day) as soon as practical, aiming to have first mobilisation within 24 hours of stroke onset **Who provided** Mobilisation was delivered by a nurse-physiotherapist team **How** Mobilisation was delivered face-to-face by a nurse-physiotherapist team **Where** In the stroke unit **When and how much** VEM began within 24 hours and continued daily for 14 days post stroke, or until discharge **Tailoring** Participants were monitored during mobilisation within the first 3 days. Mobilisation could be halted in the event of significant physiological changes **Modifications** The intervention protocol was not changed during the trial. The type and amount of mobilisation was the same for infarct and haemorrhage **How well** Planned: time-to-first mobilisation and number of minutes of mobilisation (engaged in upright activities) were recorded Actual: the median time-to-first mobilisation after symptom onset was 18.1 hours (IQR 12.8 to 21.5) in the VEM group and 30.8 hours (IQR 23.0 to 39.9) in the standard care group (P < 0.001). The total number of minutes (median, IQR) of mobilisation achieved in the VEM group was double that of standard care (VEM 167, 62 to 305, standard care 69, 31 to 115; P = 0.003)
Outcomes	Mortality

AVERT II 2008 *(Continued)*

	'Severe' adverse events 'Non-severe' adverse events Deterioration in the first 7 days Perceived exertion (Borg scale) Total dose of mobilisation Time from stroke onset to first mobilisation mRS (disability or dependency) Contamination (increase in mobility in a random sample of standard care participants) Irritability, Depression, and Anxiety (IDA) scale Assessment of Quality of Life scale
Notes	Trial ran from 2004 to 2006 Follow-up period: primary outcome 3 months, final follow-up 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used computer-generated, blocked randomization procedures with stratification by stroke severity and clinical site"
Allocation concealment (selection bias)	Low risk	Quote: "Opaque envelopes concealed the group allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were advised that they would be randomized to 1 of 2 styles of rehabilitation, A or B. Trial therapists and nursing staff could not be blinded to intervention group. To limit knowledge of VEM, interventions were conducted by dedicated trial staff out of sight of ward staff or behind closed curtains wherever possible"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All outcomes were assessed by a blinded assessor located off-site". To assess whether protocols to blind the assessor to group were effective, the blinded assessor was asked to select (forced choice) to which group they thought the participant had been allocated. This procedure was introduced in the third month of the study. A correct guess was made in 34/56 cases. This was no better than chance (P = 0.25)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 participants (2/71) lost to follow-up
Selective reporting (reporting bias)	Low risk	Primary outcome largely complete

AVERT III 2015

Methods	AVERT III was a prospective, parallel group, assessor-blind, randomized, multi-centre, international clinical trial. Participants were randomized in a ratio of 1:1 to 2 groups: 1) very early and frequent mobilisation out of bed (VEM); and 2) usual care (UC)
Participants	International, multicentre trial carried out in 56 stroke units in Australia, New Zealand, Singapore, Malaysia, and the UK (England, Scotland, Northern Ireland, and Wales) and recruiting acute stroke patients admitted to hospital within 24 hours of symptom onset 2104 participants recruited: 1054 intervention, 1050 control

AVERT III 2015 *(Continued)*

Mean age: 72.5 years
818/2104 (39%) men

258/2104 (12%) haemorrhagic
Median NIHSS 7

1170 (55%) had mild stroke (NIHSS 1 to 7)

642 (31%) moderate stroke (NIHSS 8 to 16)

291 (14%) severe stroke (NIHSS >16)

Thrombolysis treatment in 24%

Inclusion criteria:

- first or recurrent, ischaemic or haemorrhagic stroke (but not transient ischaemic attack);
- recruited within 24 hours of onset of stroke symptoms;
- aged 18 years or more;
- admitted to a stroke care unit
- must at least react to verbal commands

Exclusion criteria:

- pre-stroke disability (mRS score of 3 to 5);
- deterioration in condition in the first hour of admission resulting in admission to ICU;
- decision for palliative treatment (e.g. those with devastating stroke) or immediate surgery or concurrent diagnosis of rapidly deteriorating comorbidity;
- unstable other medical condition that is judged by the investigator to impose a hazard to the patient by involvement in the trial;
- lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol;
- concurrent recruitment to another intervention trial;
- physiological instability (systolic blood pressure less than 110, or greater than 220 mmHg, oxygen saturation < 92% with oxygen supplementation, resting heart rate < 40 or > 110 beats per minute, temperature > 38.5°C)

Treatment with rtPA was not an exclusion criteria if the attending physician permitted mobilisation to commence within 24 hours of stroke onset

Interventions

What

Materials: participant could receive usual care alone (UC) or very early and frequent mobilisation (VEM) in addition to usual care. The intervention followed a protocol (AVERT Intervention Protocol version 3, dated 25 April 2008) detailing a strict 'first time out of bed protocol'. The intervention protocol was only distributed to trial intervention staff and ethics committees in order to help maintain blinding and protect against treatment contamination in the trial. The intervention was task specific with a focus on recovery of standing and walking. The protocol allowed 4 levels of activity ranging from 4 transitions/day in severe patients (baseline NIHSS > 16) to 16 transitions/day in mild patients (baseline NIHSS 0 to 7)

Procedures: VEM participants commenced out-of-bed activity within 24 hours of stroke onset, to continue out of bed activity at a frequency and intensity guided by a detailed intervention protocol (available from the investigators)

Who provided

VEM was provided by physiotherapy and nursing staff trained in study procedures

How

VEM was provided face-to-face by physiotherapy and nursing staff

Where

AVERT III 2015 *(Continued)*

	VEM was provided in the stroke unit **When and how much** VEM began within 24 hours and lasted for 14 days or until the participant was discharged from stroke unit care. The VEM intervention included 3 key elements: 1) begin within 24 hours of stroke onset; 2) focus on sitting, standing, and walking (i.e. out-of-bed) activity; and 3) result in at least 3 out-of-bed sessions in additional to usual care. Participants assigned to VEM were assisted to continue out-of-bed activity at a dose guided by a detailed intervention protocol (see above) **Tailoring** The intervention followed a protocol that outlined the safety ranges for blood pressure, heart rate, oxygen saturation and temperature prior to first mobilisation. It advised that mobilisations should only proceed if the patient's blood pressure does not fall by > 30 mmHg on sitting up on the edge of the bed, or on getting out of bed **Modifications** The intervention protocol was not changed during the trial **How well** Planned: monitoring included time-to-first mobilisation plus number and duration of out-of-bed mobilisation sessions Actual: the VEM group was noted to have a significantly ($P < 0.01$) reduced time-to-first mobilisation from stroke onset (median 18.5 hours vs 22.4 hours) and increased median number of out-of-bed training sessions per day (6.5 vs 3) and increased median amount of out-of-bed training time per day (31 vs 10 minutes)
Outcomes	mRS at 3 months, evaluation of adverse effects, health-related quality of life, cost effectiveness and cost utility, long-term efficacy, activity limitation, dose response, patient severity, and staff injury
Notes	Trial ran from 2008 to 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A remote, web-based, computer-generated randomization procedure was used. Randomisation was balanced by site and stratified by stroke severity, based upon the patient's baseline NIHSS score
Allocation concealment (selection bias)	Low risk	All online submissions were secured by use of password and data encryption procedures. Once participant recruitment data were submitted by the site staff to the trial website (AVERT Online), the randomization allocation was immediately provided to the investigator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were aware that they could be randomized to 1 of 2 mobilisation protocols but were not provided with details. The intervention protocol was only distributed to trial intervention staff and ethics committees in order to help maintain blinding and protect against treatment contamination in the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The 3- and 12-month assessments were conducted in person or by telephone by an assessor who was remote from the location of the acute treatment of the participant and blind to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	The total number of participants missing for the primary outcome was only 21/2104 (1%)

AVERT III 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Primary outcome largely complete

Chippala 2015a

Methods	Single-blinded RCT with a blinded assessment at the end of follow-up
Participants	Acute stroke patients admitted to the stroke unit within 24 hours of symptom onset Both sexes Able to react to verbal commands Medical condition stable and physiologically stable (systolic BP 120 to 180 mmHg, oxygen saturation > 92%, heart rate 40 to 100 beats per minute, temperature < 38.5°C) 86 participants: 43 intervention, 43 control Mean age: 60 years 42/80 (52%) men 16/80 (20%) haemorrhagic 27 (34%) had mild stroke (NIHSS 0 to 7) 42 (52%) moderate stroke (NIHSS 8 to 16) 11 (14%) severe stroke (NIHSS > 16)
Interventions	**What** Materials: the trialists "adopted the AVERT Protocol. The intervention group received the following activities: sitting supported in bed, sitting unsupported out of bed, transfer with assistance, roll and sit up, sitting without support, transfer feet on the floor, standing activities, walk-early gait, and advanced gait activities" **Who provided** Not stated **How** Not stated **Where** Provided in the stroke unit **When and how much** Intervention: "The mobilisation was started (upright and out-of-bed activities) as soon as practical after the recruitment, aiming to have first mobilisation within 24 hours of the onset of the symptoms" Standard care: "Patients in the standard care group received routine stroke unit care, including the passive and active (if possible) mobilisation, correct positioning in bed, mobilisation in bed, sitting balance activities, facilitation of limb and trunk control activities, education of patient and caregiver. Both groups received standard care treatment, for 45 minutes a day, for seven days or until discharge" **Tailoring**

Chippala 2015a *(Continued)*

	"The time spent on early and frequent out-of-bed activities was determined by the patient's tolerance (5 to 30 minutes), and they received mobilisation for a minimum of two times per day for seven days or until the discharge, whichever was sooner" **Modifications** Not stated **How well** Planned: "The mobilisation was started (upright and out-of-bed activities) as soon as practical after the recruitment, which aimed to have first mobilisation within 24 hours of the onset of the symptoms. The time spent on early and frequently out-of-bed activities was determined by the patient's tolerance (5 to 30 minutes), and they received mobilisation a minimum of two times per day for seven days, or until the discharge whichever was sooner" Actual: "time to first mobilization after the symptom onset was a median 18 hours (IQR 16.62 to 19.75) in the intervention group and a median 30.5 hours (IQR 29.0 to 35) in the standard care group (P < 0.001)"
Outcomes	Primary outcome: Barthel index at the end of 3 months following the onset of stroke Length of hospital stay
Notes	Study took place March 2012 to September 2014 Reported to be a different study and patient group from Chippala 2015b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly allocated equally to either the Intervention group (very early mobilization, out of bed within 24 hours of stroke onset) or the standard care group, by the computer-generated, randomization procedures"
Allocation concealment (selection bias)	Low risk	Quote: "randomly allocated equally to either the Intervention group (very early mobilization out of bed within 24 hours of stroke onset) or the standard care group by the computer-generated, randomization procedures, using a concealed opaque envelop method. This randomization list was held by a university researcher who was not related to any part of the study"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blind, randomized controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome measurements at three-month follow-up were taken directly by the blinded assessor when the patients visited the hospital for a routine medical check-up"
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/86 (7%) missing at 3 months
Selective reporting (reporting bias)	Unclear risk	Primary outcome largely complete

Chippala 2015b

Methods	Single blinded, parallel grouped, RCT with a blinded assessment at the end of follow-up
Participants	Stroke patients admitted to the stroke unit within 24 hours of symptom onset and physician permission to mobilise within 24 hours of stroke Both sexes Able to react to verbal commands Medical condition stable and physiologically stable (systolic BP 120 to 180 mmHg, oxygen saturation > 92%, heart rate 40 to 100 beats per minute, temperature < 38.5°C) Mean age: 63.3 years 54 participants: 27 intervention, 27 control 28/49 (57%) men 11/49 (22%) haemorrhagic 27/48 (56%) had mild stroke (NIHSS 0 to 7) 21/48 (44%) moderate stroke (NIHSS 8 to 16)
Interventions	Same as Chippala 2015a Both the groups received standard care treatment including routine stroke unit care, for 45 minutes a day, for seven days, or until discharge The intervention group received VEM mobilisation activities, initiated within 24 hours of the stroke onset, in addition to the standard care. They performed early and frequent out-of-bed activities including sitting, standing, walking. The duration of mobilisation was determined by the participant's tolerance (5 to 30 minutes) with a frequency of a minimum of 2 times per day for 7 days or until the discharge, whichever was sooner
Outcomes	The mRS at 3 months. A good outcome was defined as mRS of 0 to 2 Barthel Index at 3 months Adverse events during first 3 months Length of hospital stay (days)
Notes	Study took place from September 2014 to June 2015 Reported to be a different study and patient group from Chippala 2015a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "single blinded, parallel grouped, randomized controlled trial with a blinded assessment at the end of follow-up"
Allocation concealment (selection bias)	Low risk	Quote: "randomization procedures using a concealed opaque envelop method"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blinded, parallel grouped, randomized controlled trial with a blinded assessment at the end of follow-up"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "single blinded, parallel grouped, randomized controlled trial with a blinded assessment at the end of follow-up"

Chippala 2015b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/54 (9%) missing at follow-up
Selective reporting (reporting bias)	Unclear risk	Primary outcome largely complete

Langhorne 2010

Methods	A pilot randomized trial (using a 2 x 2 factorial design) to compare conventional stroke unit procedures with more progressive (nurse-led) protocols of early mobilisation (EM), automated physiological monitoring, or both As there was no statistical interaction between the 2 protocols, the EM arms were compared directly with the normal mobilisation arms
Participants	1 stroke unit in Glasgow, Scotland Recruited 32 acute stroke patients admitted to hospital within 24 hours (and recruited within 36 hours of symptom onset) with no premorbid severe disability Of the 16 EM patients, 8 were allocated to the EM protocol alone and 8 to the EM plus automated monitoring protocols Of the 16 controls, 8 were allocated to normal mobilisation alone and 8 to normal mobilisation plus the automated monitoring protocol Mean age: 67.5 years 16/32 (50%) men 1/32 (3%) haemorrhagic Mean NIHSS 5 23 (72%) had mild stroke (NIHSS 1 to 7) 7 (22%) moderate stroke (NIHSS 8 to 16) 2 (6%) severe stroke (NIHSS > 16)
Interventions	**What** Materials: protocols for early mobilisation (VEM) or intensive physiological monitoring, or both, or standard care alone (control). VEM was planned to be similar to AVERT protocol but did not have access to the same written protocol. Procedures: the VEM protocol aimed to get participants up to sit, stand, and walk within 24 hours of the stroke and continue this at least 4 times per day Controls: the stroke unit had a philosophy of getting patients up to sit, stand, and walk early but did not have staff specifically allocated to this role. Mobilisation was normally provided by physiotherapists and nurses (30 to 60 minutes per day). Normal monitoring involved intermittent (4-hourly) checking of pulse, temperature, oxygen saturation, and blood pressure **Who provided** The research nurse had a role ensuring the VEM protocol was implemented in conjunction with physiotherapy and nursing staff **How**

Langhorne 2010 *(Continued)*

	The research nurse facilitated the VEM protocol that was largely delivered face-to-face by physiotherapy and nursing staff **Where** Provided in the stroke unit **When and how much** For 1 week after recruitment or until discharge **Tailoring** EM could be adapted according to the abilities of the participant **Modifications** Mobilisation could be halted if monitoring of pulse, temperature, oxygen saturation, or blood pressure suggested abnormal changes **How well** Planned: the EM protocol aimed to get participants up to sit, stand, and walk within 24 hours of the stroke and continue this at least 4 times per day. This was monitored as: 1) time-to-first mobilisation (attempt to get the participant out of bed, to sit, stand, or walk); 2) best level of mobilisation activity achieved (lying, sitting, standing, walking); and 3) participant activity (using automated activity monitor recordings) Actual: median time from stroke to first mobilisation in the VEM group was 27.3 hours (IQR 26.0 to 29.0) vs 32.0 hours (IQR 22.5 to 47.3) in controls (P = 0.31), however a significantly greater number of EM participants (P = 0.03) were mobilised within 1 hour of randomization. A significantly great number of EM participants (P = 0.02) achieved standing or walking when mobilisation was recorded using activity monitors
Outcomes	mRS at 3 months, adverse events, patient activity, neurological deterioration, Barthel Index at 1 week and 3 months, walking speed (1 week and discharge), patient satisfaction, resource allocation
Notes	Recruitment took place in February 2007 to January 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization sequence was to 1 of 4 nurse-led treatment protocols (2 of which delivered EM). The sequence was computer-generated in blocks of 4
Allocation concealment (selection bias)	Low risk	Quote: "patients were then randomly allocated by telephoning a secretary in an independent office who logged the patient and opened the next in a series of sequentially numbered opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were aware that they were being randomized to different care protocols. No specific measures were in place to segregate participants but recruitment did not result in participants receiving different protocols in the same ward space
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Key outcome observations were blinded to treatment allocation by using an independent assessor at day 5 and at 3 months
Incomplete outcome data (attrition bias)	Low risk	No losses after randomization

Langhorne 2010 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Primary outcome complete

Morreale 2016

Methods	Multicenter, factorial, single blind RCT
Participants	First ischaemic stroke (middle cerebral artery) 6 to 24 hours from onset Exclusion criteria included: mild stroke (NIHSS < 2), MMSE < 26, neurological or cardiovascular instability, significant comorbidity 340 participants: 220 intervention, 120 control Mean age: 64 years 246/340 (72%) men 0/340 (0%) haemorrhagic 37 (11%) had mild stroke (NIHSS 3 to 6) 260 (76%) moderate stroke (NIHSS 7 to 14) 43 (13%) severe stroke (NIHSS > 14)
Interventions	**What** A factorial design was used to compare early proprioceptive neuromuscular facilitation (PNF) or cognitive therapeutic exercise (CTE) commenced within 24 hours of admission, with delayed PNF and CTE groups, where treatment started 4 days later Materials: all physiotherapists were specifically trained for treatment protocols. Procedures: early rehabilitation: daily out-of-bed activity with either PNF or CTE commenced within 24 hours Usual care: routine hospital care for first 4 days, followed by either PNF or CTE **Who provided** Physiotherapists **How** Physiotherapists were specifically trained for treatment protocols and were not aware of the clinical features and study objective **Where** Neurology department of 2 stroke centres in Rome **When and how much** Early rehabilitation: daily out-of-bed activity (with either PNF or CTE). Dose set as 1 hour/day for first 4 days; followed by 2.25 hours/day, daily for 14 weeks; followed by 1.5 hours/day, 5 days/week until final medical follow-up (mean of 38 weeks) Usual care: routine hospital care for first 4 days, followed by either PNF or CTE. Dose based on standard hospital care for first 4 days, and (from day 5) as per early rehabilitation groups **Tailoring**

Morreale 2016 *(Continued)*

	Not stated **Modifications** Not stated **How well** Planned: a physical therapists' co-ordinator monitored the adherence to and homogeneity of treatment protocols in all settings Actual: not reported
Outcomes	Primary outcome measures were disability (mRS and Barthel Index) at 3 and 12 months Secondary outcomes: • safety - immobility-related adverse events at 3 and 12 months. • Six Minute Walking Test • Motricity index • MMSE • Beck Depression Inventory
Notes	Trial ran between January 2008 and January 2013 Loss to follow-up was not divided by group 3 months: 13 dead, 25 'lack of compliance' 12 months: 16 dead, 27 'lack of compliance', 4 recurrent stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence in blocks of 4 to 1. A factorial design was used to compare early proprioceptive neuromuscular facilitation (PNF) or cognitive therapeutic exercise (CTE) commenced within 24 hours of admission, with delayed PNF and CTE groups, where treatment started 4 days later Randomisation was stratified by age, sex, risk factors, stroke aetiology, side, NIHSS score
Allocation concealment (selection bias)	Unclear risk	Quote: "..physical therapists' coordinator randomly assigned all patients..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "All physiotherapists were specifically trained for treatment protocols and were unaware of clinical features....and study objective"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All scales at 3 and 12 months were administered by "two different neurologists who were blinded for treatment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	25/340 (7%) of participants were lost to follow-up at 3 months and 27/340 (8%) at 12 months due to 'lack of compliance'

Morreale 2016 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Primary outcome largely complete

Morreale 2016 CTE

Methods	Cognitive therapeutic exercise (CTE) subgroup of Morreale 2016
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Morreale 2016
Allocation concealment (selection bias)	Unclear risk	See Morreale 2016
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Morreale 2016
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See Morreale 2016
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Morreale 2016
Selective reporting (reporting bias)	Unclear risk	See Morreale 2016

Morreale 2016 PNF

Methods	Neuromuscular facilitation (PNF) subgroup of Morreale 2016
Participants	
Interventions	
Outcomes	
Notes	

Morreale 2016 PNF *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Morreale 2016
Allocation concealment (selection bias)	Unclear risk	See Morreale 2016
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Morreale 2016
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See Morreale 2016
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Morreale 2016
Selective reporting (reporting bias)	Unclear risk	See Morreale 2016

Poletto 2015

Methods	Quote: "randomized, controlled, single-blind clinical trial compared early mobilization (within 48 h of symptom onset) with routine physical therapy"
Participants	Quote: "adult patients with CT- or MRI-confirmed ischemic stroke within 48 h of symptom onset who were admitted on weekdays from March to November 2012 to the acute vascular unit or general emergency unit of a large urban emergency department" 39 participants: 19 intervention, 20 control Mean age: 65 years 13/37 (35%) men 0/37 (0%) haemorrhagic Mean NIHSS score of 10.5 11 (30%) had mild stroke (NIHSS 0 to 5) 12 (32%) moderate stroke (NIHSS 6 to 11) 14 (38%) severe stroke (NIHSS > 11)
Interventions	**What** Materials: unclear for staff but "patients and their families received a manual developed for the study, with guidance on positioning in bed and posture shifting to use at home after discharge" Procedures: these "focused on getting out of bed, sitting in a chair, or standing (whenever and as soon as possible), and conducting functional training and motor relearning, pursuant to the Bobath concept. Exercises were performed bilaterally with at least 5 repetitions for each joint and each exercise, with emphasis on deficits on the impaired side. In addition, patients and their families received a manual

Poletto 2015 *(Continued)*

developed for the study, with guidance on positioning in bed and posture shifting to use at home after discharge. Intervention patients were mobilized 5 times a week, once a day, for approximately 30 min per session, in addition to sitting out of bed for at least 30 min whenever possible"

Controls: they received "conventional physical therapy performed when requested by the staff. Therapy varied according to the patients' needs and the availability of physical therapists but generally included global motor exercises and respiratory therapy (ordinarily in bed). The duration of standard-care therapy sessions was approximately 15 min"

Who provided

Quote: "The program was carried out by trained physical therapists"

How

Quote: "The program was carried out by trained physical therapists"

Where

The acute vascular unit or general emergency unit of a large urban hospital in Brazil.

When and how much

Quote: "Exercises were performed bilaterally with at least 5 repetitions for each joint and each exercise, and emphasis on deficits on the impaired side. Intervention patients were mobilized 5 times a week, once a day, for approximately 30 min per session, in addition to sitting out of bed for at least 30 min whenever possible". "Sessions were held until hospital discharge or the 14th treatment day, whichever occurred first, regardless of where the patient was located"

Tailoring

Not stated

Modifications

Not stated

How well

Planned: "The session duration (in minutes) and number of sessions were recorded. Sessions were held until hospital discharge or the 14th treatment day, whichever occurred first, regardless of where the patient was located"

Actual: "Intervention patients received mobilization earlier and more frequently than controls (table 2). The median time from stroke to first mobilization was 43 h (vs. 72 h in the CG), and the total duration of mobilization during the hospitalization period was 135 min (IQR 85 to 213; vs. 0 min in the CG (IQR 0 to 50)). Only 2 patients did not initiate early mobilization (within 48 h) in the IG. Moreover, only 5 patients in the CG (26%) received physical therapy during hospitalization, with an average duration of 15 min per session. After hospital discharge, 57% of the patients in the IG and 37% in the CG underwent physical therapy sessions (P = 0.28). IG patients had more out-of-bed activities compared with controls (4.3 vs 0.3), initiating activities while still in the ED. Only the 5 patients who received physical therapy in the CG left their beds; all other controls remained bedbound during hospitalization"

Outcomes	The trialists "sought only to evaluate the feasibility and safety of the intervention. The primary outcome measures were functional capacity (mRS score 0 to 2) and mortality at 3 months. Feasibility endpoints were (a) time-to-first mobilisation, and (b) total duration of motor physical therapy. Safety endpoints were: (a) complications during early mobilisation (first 48 h), i.e. symptomatic hypotension (syncope or presyncope) or neurological deterioration (defined as any worsening in NIHSS score); (b) falls during hospitalisation and within 3 months of stroke; (c) complications related to immobility (pneumonia, pulmonary embolism, and deep vein thrombosis) at 3 months, and (d) death within 3 months.

Poletto 2015 *(Continued)*

	Secondary outcomes were measured at 3 months (mRS score 0 to 1, mRS score 0 to 2, mean NIHSS score, and mBI ≥ 85)".
Notes	ClinicalTrials.gov NCT01694992 Reported as a pilot RCT that recruited from March to November 2012. Planned recruitment was for 174 participants (82 per group) but was limited by slow recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed online (randomization.com) by a study investigator, using a randomization plan stratified by blocks of varying sizes (blocks of 2, 4, or 6)"
Allocation concealment (selection bias)	Low risk	Quote: "randomly allocated to an intervention group (IG) or a control group (CG), with the allocation records stored in opaque, sealed, and sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were informed that they would begin physical therapy on the first day of assessment (IG) or follow the hospital routine (CG)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Baseline and postintervention measures were performed by a study investigator who remained blinded to group allocation. To ensure blinding of any monitoring neurologists, no notes of group allocation were made in the hospital's electronic medical record".
Incomplete outcome data (attrition bias) All outcomes	High risk	6/39 (15%) missing at 3 month follow-up
Selective reporting (reporting bias)	Low risk	Primary outcome largely complete

SEVEL 2016

Methods	Prospective multicenter RCT testing 2 sitting procedures at the acute phase of ischaemic stroke
Participants	Acute ischaemic stroke patients recruited from 11 centres in the North West region of France Participants were: over 18 years age, had neurological deficits, haemorrhage excluded on imaging, enrolled in a healthcare plan (French social security) Exclusions included; very mild (NIHSS < 3) or very severe stroke (NIHSS > 22), reduced consciousness Glasgow Coma Score < 13), fluctuating neurological signs (history of worsening linked to an upright positioning), known symptomatic intra-cranial stenosis > 50%, vomiting or difficulty in breathing, contraindication for sitting, e.g. deep vein thrombosis or lower limb fracture, prior dependency Rankin score 3 to 6, anticipated difficulty in follow-up 167 participants: 82 intervention, 85 control Mean age: 70 years 89/138 (64%) men 0/138 (0%) haemorrhagic

SEVEL 2016 *(Continued)*

	Mean NIHSS 7.5 76 (56%) had mild stroke (Rankin score 0 to 3) 45 (34%) moderate stroke (Rankin score 4) 13 (10%) severe stroke (Rankin score 5)
Interventions	**What** This study aimed to test 2 different protocols for sitting in acute ischaemic stroke patients. Early protocol: participants seated out of bed at the earliest time possible, ideally the day of stroke onset (day 0) and no later than the calendar day after stroke onset Progressive protocol: the participant would be positioned in bed at 30°, 45° the day after (day 1), and 60° at day 2, and sitting out of bed at day 3 (which corresponds to the first sitting in this group). Those angles reflect the position of the upper body relative to the bed (and floor) **Who provided** The physiotherapist or the nurses were in charge of collecting the data (e.g. blood pressure, tolerance) related to the protocol **How** For both protocols, minimal duration of the first sitting was 15 minutes. The procedure could be continued, depending on participant fatigue and tolerance (60 minutes maximum). The physiotherapist or the nurses were in charge of collecting the data (blood pressure, tolerance. . .) related to it. Sitting posture (legs dangling or feet positioned on a foot rest), was done as usual, in keeping with each unit's protocol. The use of a lifter, when necessary, was allowed **Where** Stroke centres of 11 hospitals in North West France **When and how much** For both protocols, minimal duration of the first sitting was 15 minutes. The procedure could be continued, depending on patient fatigue and tolerance (60 minutes maximum). Sitting was repeated on a daily basis according to initial tolerance of the procedure, as approved by the physician in charge **Tailoring** Close monitoring of blood pressure and heart rate was performed: before the sitting procedure, immediately after, and 5 minutes after. While sitting, participants showing any sign of low tolerance, defined by neurological worsening (of current or new neurological deficits), vagal reaction (bradycardia or nausea), a greater than 40 mmHg increase of blood pressure topping 180/100 mmHg, or a symptomatic decrease in blood pressure, would be put back in bed. Sitting was repeated on a daily basis according to initial tolerance of the procedure, as approved by the physician in charge **Modifications** While sitting, participants showing any sign of low tolerance, defined by neurological worsening (of current or new neurological deficits), vagal reaction (bradycardia or nausea), a greater than 40 mmHg increase of blood pressure topping 180/100 mmHg, or a symptomatic decrease in blood pressure, would be put back in bed **How well** Planned: the early protocol intended that participants would be seated, out of bed, at the earliest time possible, no later than the calendar day after stroke onset. In the progressive protocol, the participant would be positioned in bed at 30°, 45° the day after (day 1), and 60° at day 2, and sitting out of bed at day 3 (which corresponds to the first sitting in this group)

SEVEL 2016 *(Continued)*

	Actual: time from stroke to the first sitting time was 1.1 ± 0.2 days in the early sitting group versus 3 ± 0.2 days in the progressive group First sitting lasted significantly longer in the progressive group compared to the early group: 83.7 ± 94.7 minutes versus 56.6 ± 41.7 minutes respectively (P < 0.05). Tolerance of the sitting procedure was the same in the early and progressive sitting groups, with a prevalence of side effects of 14.5% and 13.7%, respectively. Sitting was continued daily for both groups during hospitalisation in 96% of cases. NB: a small amount of out-of-bed activity was incorporated in transferring between bed and chair, which started 2 days earlier in the intervention group than the standard care group Physiotherapy and deep vein thrombosis prevention by low molecular weight heparin were performed as usual in each unit
Outcomes	The primary outcome measure was the proportion of mRS 0 to 2 at 3 months visit after stroke onset Secondary outcomes were assessed at 7 days (or the day of discharge, if before 7 days), and the 3-month follow-up and included: • NIHSS score, Rankin score, Barthel score; • data about the tolerance of the sitting positioning (including prevalence of side effects that forced termination of the procedure); • length of hospitalisation; • complications that occurred during hospital stay were reviewed at 3 months using a multiple-choice list, and based on both participant interview and medical records; • duration of sitting out of bed was calculated from the recorded time at which the participant was positioned seated out of bed to the time at which the participant would be put back in bed
Notes	SEVEL (Stroke and Early VErticaL positioning) study clinicaltrials.org registration number NCT01573299 The enrolment period covered November 2011 to April 2014. The study ended prematurely (after 167 of a target of 400) as it became unviable, due to the slow recruitment rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The random sequence was generated by our statistician (CV) using the SAS software"
Allocation concealment (selection bias)	Low risk	Randomisation between the early and progressive sitting groups was performed via "numbered sealed envelopes that the investigator would draw from, in consecutive fashion (with blocks of 4 in 1:1 ratio, stratified by center) each time a patient was enrolled in the study" Quote: "Data were reported online using a server dedicated to the study"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Evaluations were made during the intermediate time point at 7 days (or the day of discharge, if before 7 days) and at 3 months after stroke, by a neurologist from the same stroke unit, aware of the study and unblinded to the patient group assignment"
Incomplete outcome data (attrition bias)	High risk	Substantial drop out (29/167; 17%) after randomization

SEVEL 2016 *(Continued)*

All outcomes		Participants with major deviation to the protocol or serious adverse event that were enrolled but could not continue the study were assigned a Rankin score in the category 3 to 6
Selective reporting (reporting bias)	Unclear risk	Primary outcome largely complete

Sundseth 2012

Methods	Prospective RCT with blinded assessment at follow-up
Participants	1 stroke unit in Akershus, Norway Acute stroke patients (infarct or haemorrhage), defined according to the WHO criteria, admitted to the stroke unit within 24 hours of stroke Exclusion criteria included; age < 18 years, prior dependency (mRS score 1 to 5), secondary haemorrhage, acute coronary disease, treated with thrombolysis or thrombectomy 65 participants recruited (12 lost to follow-up): 32 intervention (7 lost after randomization), 33 control (5 lost after randomization) Mean age: 77 years 25/56 (45%) men 5/56 (18%) haemorrhagic Mean NIHSS 8 37 (66%) had mild stroke (NIHSS 1 to 7) 11 (20%) moderate stroke (NIHSS 8 to 16) 8 (14%) severe stroke (NIHSS > 16) Significantly lower prevalence of diabetes in the intervention group: 2/27 (7%) vs 8/29 (28%); P = 0.05
Interventions	**What** Materials: both groups received standard stroke unit care. No detailed mobilisation protocol was used. Procedures: VEM participants were mobilised out of bed as soon as possible after randomization and at least 24 hours from admission to hospital. Mobilisation, meaning all out-of-bed activities, was carried out several times per day. Control participants started mobilisation 24 to 48 hours from admission **Who provided** VEM was performed by physiotherapists, nursing staff, and occupational therapists **How** VEM participants were mobilised out of bed as soon as possible after randomization and at least 24 hours from admission to hospital by physiotherapy, nursing, and occupational therapy staff **Where** In the stroke unit **When and how much** Until discharge from the stroke unit **Tailoring**

Sundseth 2012 *(Continued)*

	All mobilisation was adjusted to the participant's needs and abilities. A neurologist could be called to postpone mobilisation in participants with deteriorating condition while exercising **Modifications** The intervention protocol was not changed during the trial. The type and amount of mobilisation was the same for infarct and haemorrhage **How well** Planned: the type and amount of mobilisation was similar to the VEM group but neither time nor duration was recorded Actual: 5/32 VEM participants were not mobilised to protocol (3 were mobilised within 48 hours and 2 within 72 hours) 1/33 control participant had very delayed mobilisation at 85 hours. Median time from stroke to first mobilisation in the VEM group was 13.1 hours (IQR 8.5 to 25.6) vs 33.3 hours (IQR 26.0 to 39.0) in controls (P = 0.001). Neither frequency nor duration of mobilisation was recorded

Outcomes	Outcomes were recorded at discharge and 3 months and included:
	
	• good outcome (mRS of 0 to 2);
	• survival;
	• ADL score (Barthel index);
	• Complications were classified as:
	  * stroke-related (recurrent stroke or intracerebral haemorrhage, transient ischaemic attack, post-apoplectic epilepsy)
	  * immobility-related (deep vein thrombosis, pulmonary embolism, bedsores, pneumonia, urinary tract infection, and falls); and comorbidity-related (angina pectoris, myocardial infarction)
	  * Hospital Anxiety and Depression Scale (HADS)

Notes	Study recruited during 2007 and 2009 to 2010. Additional activity was not specified, but the intervention group participants appeared to have received more out-of-bed activity in total, because it commenced earlier. Study was powered to include 246 participants, but stopped early because of slow recruitment 9 participants were excluded after randomization when the diagnosis of stroke could not be confirmed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated, blocked, randomization procedures"
Allocation concealment (selection bias)	Low risk	Quote: "using opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No specific comment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded assessment at the end of follow-up". Blinding was not present for earlier outcomes
Incomplete outcome data (attrition bias)	Unclear risk	A total of 12/65 (18%) patients randomized did not undergo 3-month follow-up

Sundseth 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Primary outcome largely complete

ADL: activities of daily living
BP: blood pressure
ICU: intensive care unit
IQR: interquartile range
MMSE: Mini Mental State Examinsation
mRS: modified Rankin scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomized controlled trial
rtPA: recombinant tissue plasminogen activator
VEM: very early mobilisation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AMOBES 2017	Commenced mobilisation after 48 hours
Asberg 1989	Insufficient details to confirm eligibility
Chu 2003	Timing not stated
Di Lauro 2003	No time difference between groups
Diserens 2010	Commenced mobilisation after 52 hours
Duan 2006	Timing not stated, additional psychotherapy and cognitive therapy
Fang 2001a	Rehabilitation started 0-7 days after onset
Fang 2001b	Rehabilitation started within 7 days of onset
Gong 2003	Timing not stated, not randomised
Gorbunov 2003	Insufficient details to confirm eligibility
Gu 2006	Timing not stated
Guan 2001	Timing not stated, confounded by additional psychotherapy and swallowing therapy
Hamrin 1982	Confounded by rehabilitation package (a large number of components of stroke unit care versus none), pseudo-RCT
Hara 2001	Insufficient details to confirm eligibility
Huang 2001	Timing not stated
Huang 2003	Therapy was started < 1 day (ischaemic) or < 3 days (haemorrhagic) Both types of participants were analysed together as a group Contact attempted for further details - this was unsuccessful
Ishida 2001	Uncertain methods - major imbalance in groups

Study	Reason for exclusion
Kreisel 2005	No time difference of therapy between groups
Li 1999	No details on timing
Li 2003	Timing not stated
Li 2004	Timing not stated
Lin 2005	Timing not stated, confounded by additional psychotherapy, cognitive therapy
Liu 2001b	Rehabilitation started at 3 days
Liu 2003b	Rehabilitation started at 3-5 days
Liu 2004	No control < 48 hours, confounded by additional functional electrical stimulation
Marshall 2011	Insufficient details to confirm eligibility
Miskovic 2004	Insufficient details to confirm eligibility
Pan 2004	Timing not stated
Qian 2003	Timing not stated
Qian 2004	Timing not stated
Raicevic 2000	Timing not stated Possibly passive therapies - not mobilisation
Richards 1993	Gait rehabilitation began in first 7 days
Sankara Kumaran 2013	Not formally randomised - purposive sampling
Song 2005	Timing not stated
Sun 2002	Insufficient details to confirm eligibility
Toyota 2001	Not clearly randomised (major imbalance in groups)
Truscott 1974	Not an RCT (observational)
Wang 2004	Timing uncertain - recruited after stabilisation
Wang 2005	Treatment within 1 week of onset
Wang 2006	Rehabilitation began at 10-20 days
Wu 2012	Delayed mobilisation - began on day 3
Xi 2003	Quasi-randomised, uncertain when out of bed
Xiao 2000	Delayed mobilisation - recruited at day 3
Xiao 2004	Timing not stated

Study	Reason for exclusion
Xie 2003a	Began at 6-52 hours
Xue 2004	Intervention was the earlier delivery of a rehabilitation package that included mobilisation and other therapies considered to potentially confound the results (speech therapy, swallowing therapy, psychological therapy including anti-depressants)
Xue 2006	Rehabilitation training began at 24 hours to 3 days
Xue 2008	Abstract only - no details on timing
Zeng 2004	Confounded by Chinese medicine, timing uncertain, quasi-randomised
Zhang 1998	Timing not stated
Zhang 2001	Began after 48 hours. Content uncertain
Zhao 2003	Uncertain timing: "as soon as state of illness was stable"
Zheng 2004a	Began 3-7 days after stroke

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Izumi 2001

Methods	Quote "RCT"
Participants	Early rehabilitation
Interventions	Uncertain timing of onset
Outcomes	
Notes	No further details

Liu 2010e

Methods	Prospective multicenter, randomized controlled study, comparing standard care (SC) vs standard care plus early rehabilitation (VER: rehabilitation as soon as practical after randomization but within 48 hours of symptom onset)
Participants	Patients presenting < 48 hours after ICH (a first time ICH confirmed by MRI or CT) to the neurology wards or rehabilitation units of participating hospitals with no contraindications to being mobilised within 48 hours of stroke onset
Interventions	VER: participants commenced rehabilitation within 48 hours of ICH onset SC group commenced rehabilitation after 7 days. Within the first week this involved bed rest or sitting in a chair. There is no showering or active rehabilitation with the main focus being medical management. Standard rehabilitation is usually commenced 1 week after stroke admission and continues until discharge. It is performed by the participant's relatives under the guidance of medical staff and

Liu 2010e *(Continued)*

	usually involves 1) exercises of daily living, stretching exercises, and neuromuscular electric stimulation, and 2) functional training in which the participants are instructed to do repetitive and systematic practice of tasks, such as stirring, grasping, and pointing
Outcomes	Death, Barthel Index, SF-36, complications
Notes	Although rehabilitation started within 48 hours it appears to have been initially 'passive'. As yet we have been unable to obtain further details from the authors.

Nilsson 2003

Methods	Uncertain
Participants	
Interventions	
Outcomes	
Notes	Abstract only - no details

Skevin 2009

Methods	Uncertain
Participants	Stroke patients within 24 hours
Interventions	Early rehabilitation programme
Outcomes	
Notes	Abstract only - no clinical outcomes

Song 2010

Methods	Single-blinded, RCT
Participants	Early stroke
Interventions	Early rehabilitation
Outcomes	
Notes	Uncertain timing - trying to obtain full report

Xu 2001

Methods	Uncertain

Xu 2001 *(Continued)*

Participants	
Interventions	Early progressive physiotherapy
Outcomes	
Notes	Abstract only

Zheng 2004

Methods	Uncertain
Participants	
Interventions	
Outcomes	
Notes	Unable to obtain abstract

Zielke 2003

Methods	Uncertain
Participants	
Interventions	
Outcomes	
Notes	No details available

CT: computed tomography
ICH: intracerebral haemorrhage
MRI: magnetic resonance imaging
RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

AVERT-DOSE 2017

Trial name or title	AVERT-DOSE (Determining Optimal early rehabilitation after StrokE): a multi-arm covariate-adjusted, response-adaptive randomized controlled trial
Methods	Multicentre RCT
Participants	Acute stroke patients (within 48 hours after stroke)
Interventions	Early mobility rehabilitation protocols informed by the world's first global trial of early rehabilitation (AVERT)

AVERT-DOSE 2017 *(Continued)*

Outcomes	Rankin score
Starting date	Proposal at planning stage (2018 to 2022)
Contact information	Julie Bernhardt, Florey Institute of Neuroscience and Mental Health, Melbourne, Australia
Notes	

ChiCTR-ICR-15005992

Trial name or title	Effect of early and intensive rehabilitation on functional recovery after stroke
Methods	Randomised parallel controlled comparison of 2 levels of early rehabilitation compared with conventional rehabilitation
Participants	Ischaemic stroke available for randomization within 24 hours of symptom onset
Interventions	2 levels of early rehabilitation compared with conventional rehabilitation
Outcomes	MRI scan, NIHSS score, Fugl-Meyer Assessment Scale, Rivermead Motor Assessment Scale, Barthel Index
Starting date	
Contact information	
Notes	Yanna Tong, Department of Neurology , Beijing Luhe Hospital, Capital Medical University, Tongzhou District, Beijing, China tongyanna@163.com +86 13426364922

ChiCTR-IPR-16008652

Trial name or title	Efficacy and safety of very early rehabilitation within 24 hours of ischemic stroke with small-artery occlusion
Methods	RCT
Participants	Inclusion criteria: patients 18 years or older consecutively admitted to the stroke unit within 24 hours after stroke onset were screened for recruitment. Patients with cerebral infarction and small artery occlusion, defined according to the World Health Organization definition, were all included Exclusion criteria: patients with mRS score ≥ 1 on admission; patients who were unable to complete the baseline survey because of serious aphasia, language difficulties, or cognitive deficits; patient with other medical conditions, such as severe heart failure, acute coronary syndrome, which prevented early rehabilitation; and patients who were unable to provide informed consent
Interventions	Very early rehabilitation (within 24 hours) versus early rehabilitation
Outcomes	NIHSS; Fugl-Meyer Assessment; Barthel Index; mRS
Starting date	2016
Contact information	shoufengliu2010@163.com

ChiCTR-IPR-16008652 *(Continued)*	6 Jizhao Road, Jinnan District, Tianjin, China Telephone: +86 022-59065182 Email: shoufengliu2010@163.com Affiliation: Tianjin Huanhu Hospital
Notes	Aim to recruit 2 groups of 50 participants each

ChiCTR-TRC-08000201	
Trial name or title	The effect of early mobilisation for stroke patients
Methods	Randomised trial
Participants	The effect of early mobilisation for stroke patients
Interventions	VEM (within 48 hrs) vs early mobilisation (1 week) after stroke
Outcomes	
Starting date	
Contact information	
Notes	Onging with at least 150 participants planned

mRS: modified Rankin scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomized controlled trial
VEM: very early mobilisation

DATA AND ANALYSES

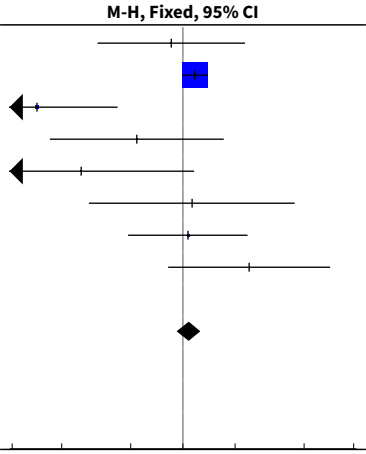
Comparison 1. Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or poor outcome	8	2542	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]
2 Death	8	2561	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.95, 1.70]
3 Death or dependence (modified Rankin score 3 to 6)	8	2542	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]
4 Death or institutional care	3	227	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.53, 2.07]
5 Activities of daily living (ADL) score	9	2630	Mean Difference (IV, Random, 95% CI)	1.94 [0.75, 3.13]

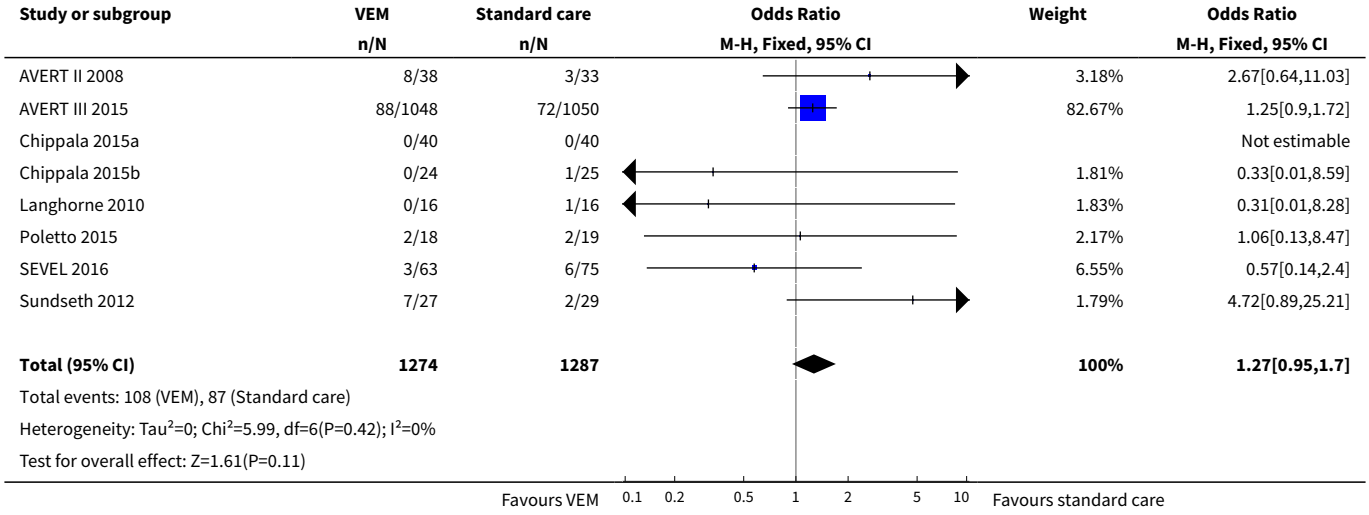
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Subjective Health Status score	1	68	Mean Difference (IV, Random, 95% CI)	0.07 [-0.10, 0.23]
7 Able to walk	4	2255	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.21]
8 Mobility score	2	102	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.27, 0.56]
9 Any complication: participants who experienced at least one complication	7	2778	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.06]
10 Type of complication: participants who experienced at least one complication	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Complications of immobility	7	2778	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.03]
10.2 Other complications	6	2435	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.23]
11 Mood score	2	100	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.33, 0.46]
12 Length of acute hospital stay (days)	8	2551	Mean Difference (IV, Random, 95% CI)	-1.44 [-2.28, -0.60]

Analysis 1.1. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 1 Death or poor outcome.

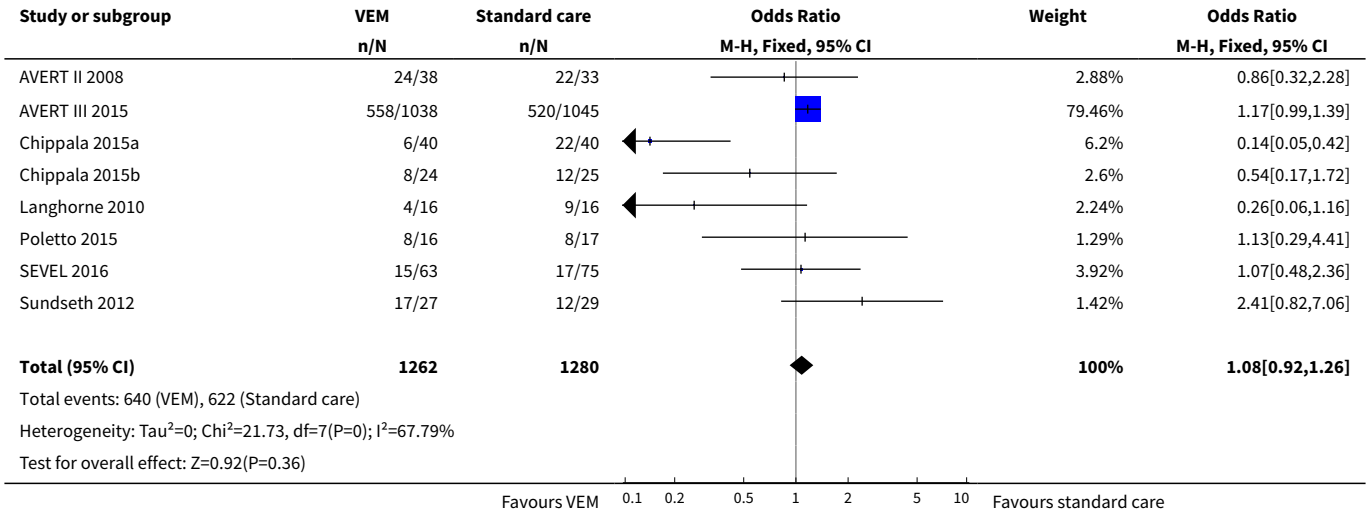
Study or subgroup	VEM n/N	Standard care n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AVERT II 2008	24/38	22/33		2.88%	0.86[0.32,2.28]
AVERT III 2015	558/1038	520/1045		79.46%	1.17[0.99,1.39]
Chippala 2015a	6/40	22/40		6.2%	0.14[0.05,0.42]
Chippala 2015b	8/24	12/25		2.6%	0.54[0.17,1.72]
Langhorne 2010	4/16	9/16		2.24%	0.26[0.06,1.16]
Poletto 2015	8/16	8/17		1.29%	1.13[0.29,4.41]
SEVEL 2016	15/63	17/75		3.92%	1.07[0.48,2.36]
Sundseth 2012	17/27	12/29		1.42%	2.41[0.82,7.06]
Total (95% CI)	**1262**	**1280**		**100%**	**1.08[0.92,1.26]**
Total events: 640 (VEM), 622 (Standard care)					
Heterogeneity: Tau^2=0; Chi^2=21.73, df=7(P=0); I^2=67.79%					
Test for overall effect: Z=0.92(P=0.36)					



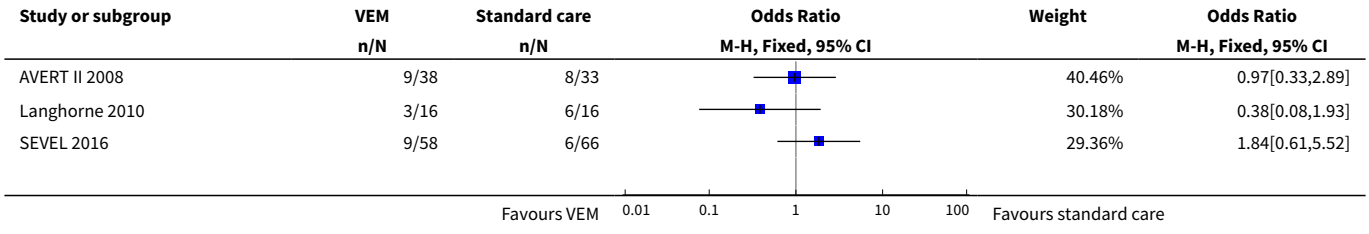
Analysis 1.2. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 2 Death.

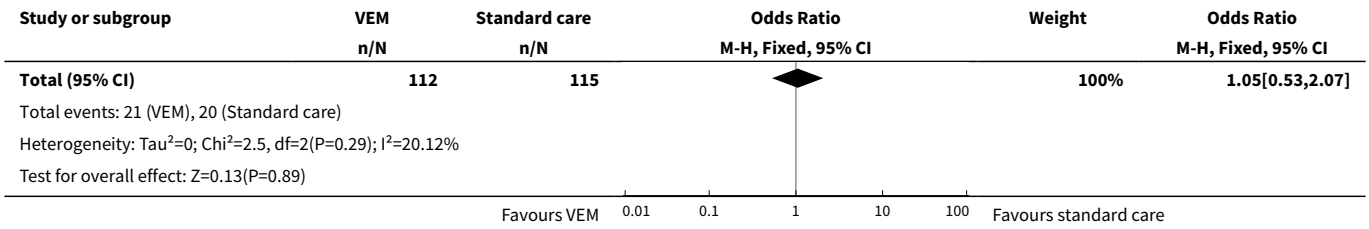


Analysis 1.3. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 3 Death or dependence (modified Rankin score 3 to 6).

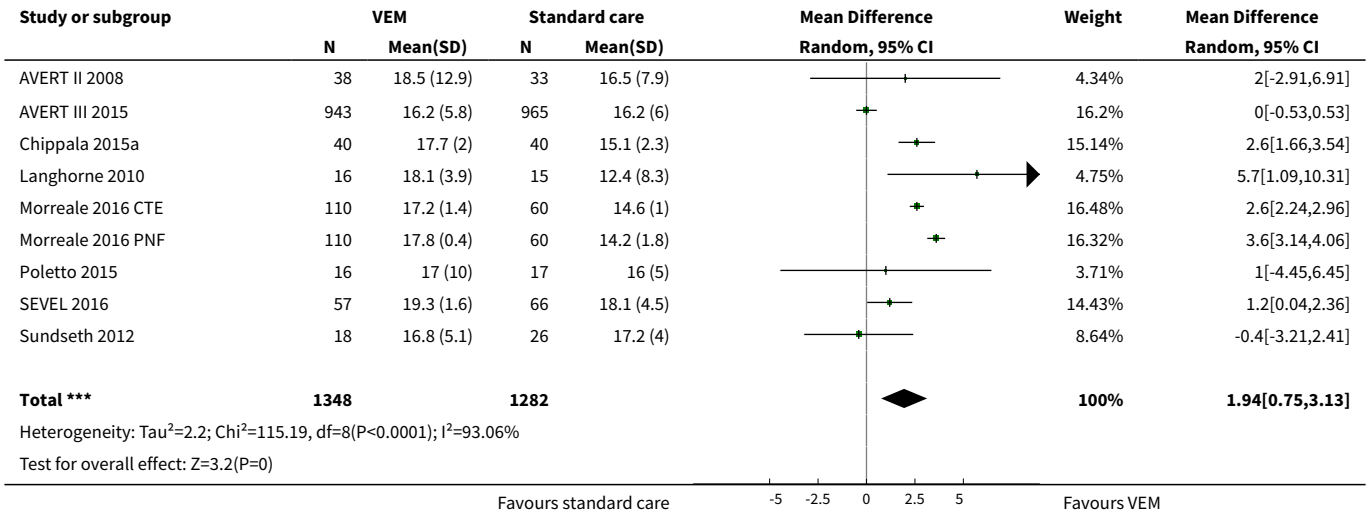


Analysis 1.4. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 4 Death or institutional care.

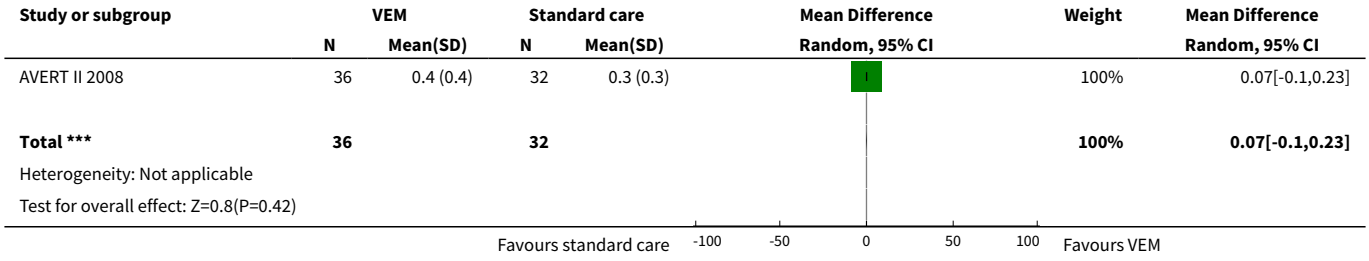




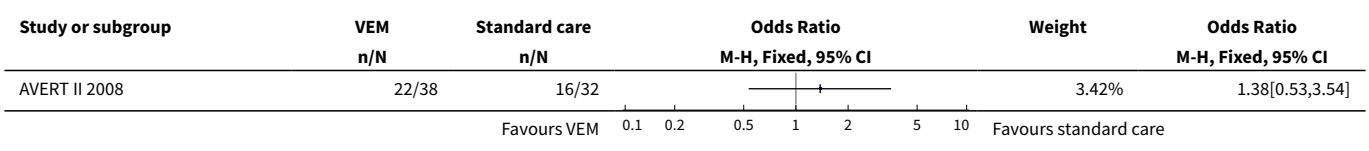
Analysis 1.5. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 5 Activities of daily living (ADL) score.

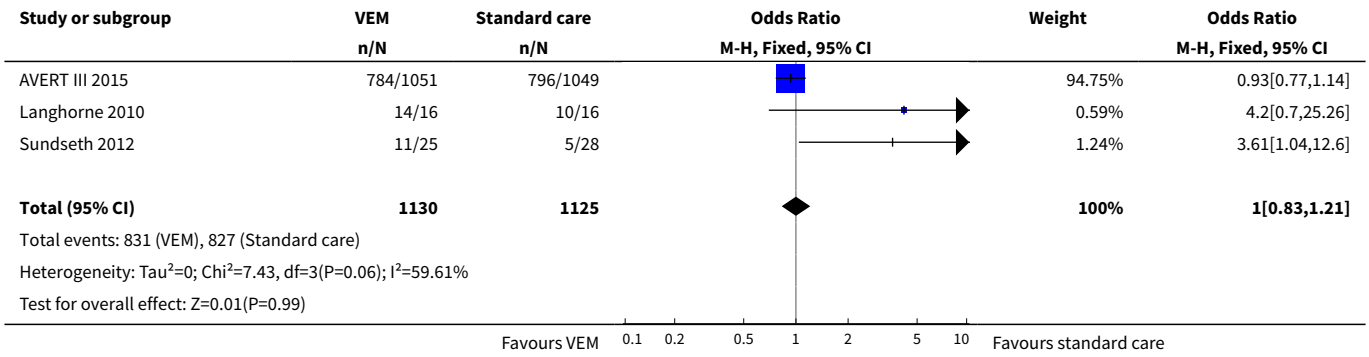


Analysis 1.6. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 6 Subjective Health Status score.

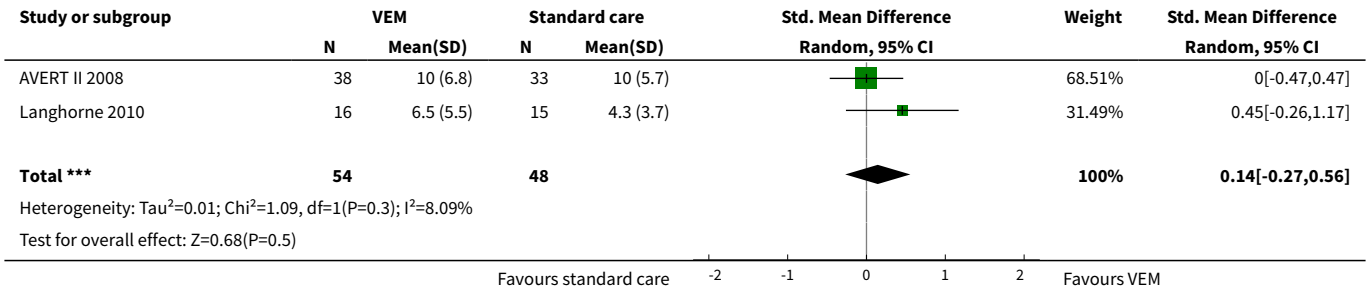


Analysis 1.7. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 7 Able to walk.

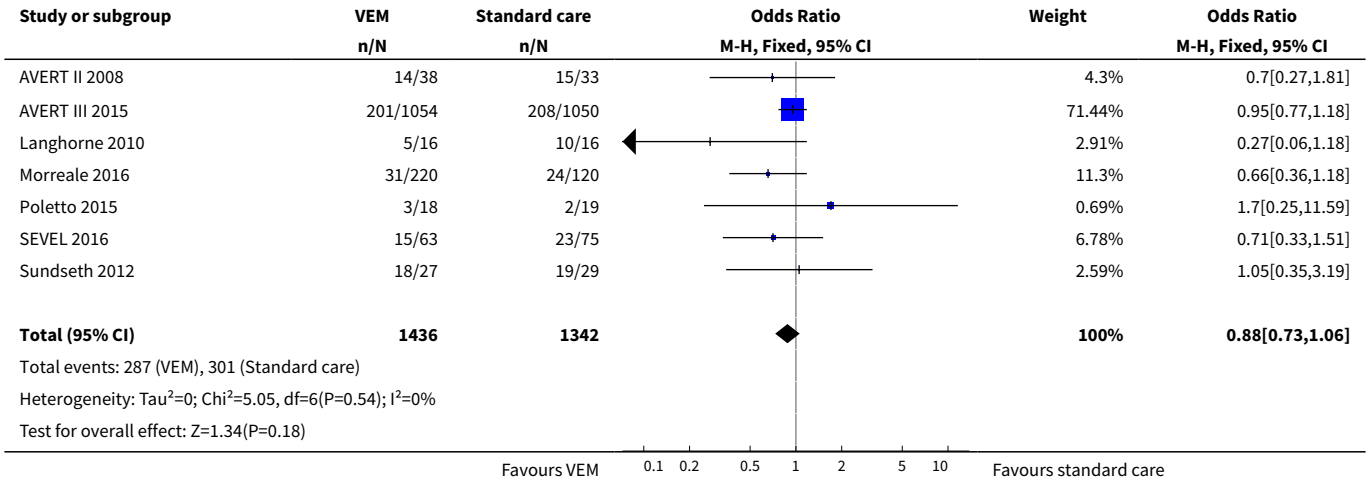




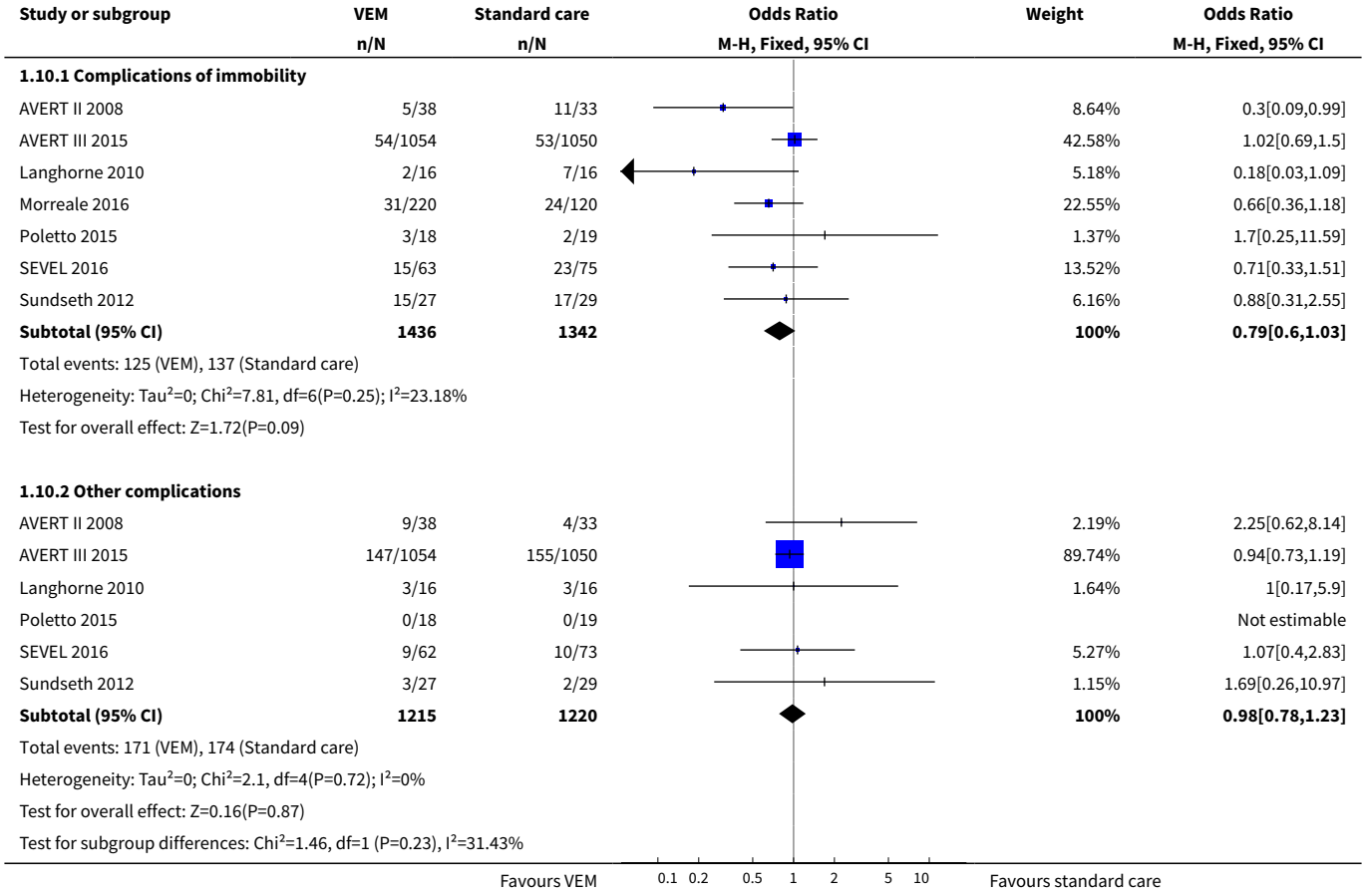
Analysis 1.8. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 8 Mobility score.



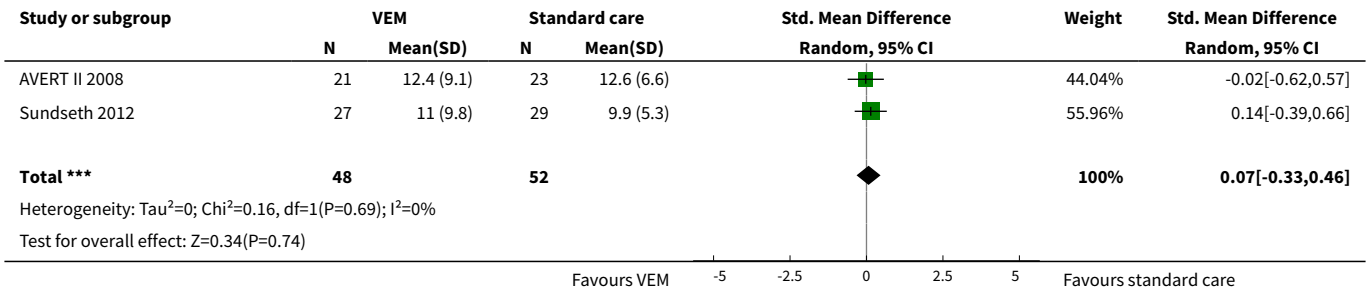
Analysis 1.9. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 9 Any complication: participants who experienced at least one complication.



Analysis 1.10. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 10 Type of complication: participants who experienced at least one complication.



Analysis 1.11. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 11 Mood score.

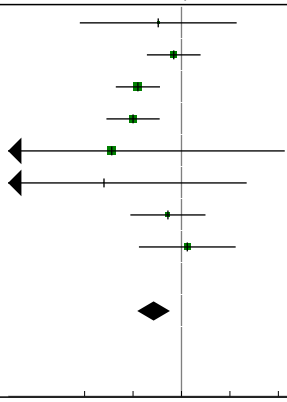


Analysis 1.12. Comparison 1 Very early mobilisation (VEM) versus standard care (measured at end of scheduled follow-up), Outcome 12 Length of acute hospital stay (days).

Study or subgroup	VEM N	VEM Mean(SD)	Standard care N	Standard care Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
AVERT II 2008	38	8.6 (9.4)	33	9.8 (8)		4.01%	-1.2[-5.25,2.85]
AVERT III 2015	1052	11.6 (16.3)	1050	12 (16.1)		21.75%	-0.4[-1.79,0.99]
Chippala 2015a	40	8 (1.4)	40	10.3 (3.4)		26.84%	-2.25[-3.39,-1.11]
Chippala 2015b	24	8.7 (1.4)	25	11.2 (3.2)		21.96%	-2.5[-3.87,-1.13]
Langhorne 2010	16	11.3 (9.9)	16	14.9 (15.3)		0.88%	-3.6[-12.53,5.33]
Poletto 2015	18	9 (6.4)	19	13 (15)		1.28%	-4[-11.36,3.36]
SEVEL 2016	58	9.8 (4.9)	66	10.5 (6.1)		13.92%	-0.7[-2.64,1.24]
Sundseth 2012	27	10.2 (4.2)	29	9.9 (5.3)		9.38%	0.3[-2.2,2.8]
Total ***	**1273**		**1278**			**100%**	**-1.44[-2.28,-0.6]**

Heterogeneity: Tau^2=0.35; Chi^2=9.44, df=7(P=0.22); I^2=25.84%

Test for overall effect: Z=3.35(P=0)

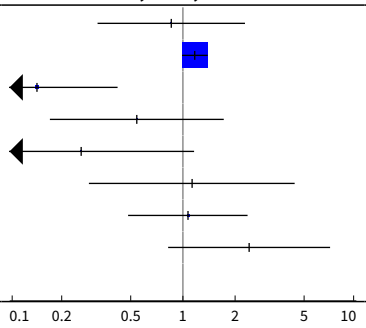


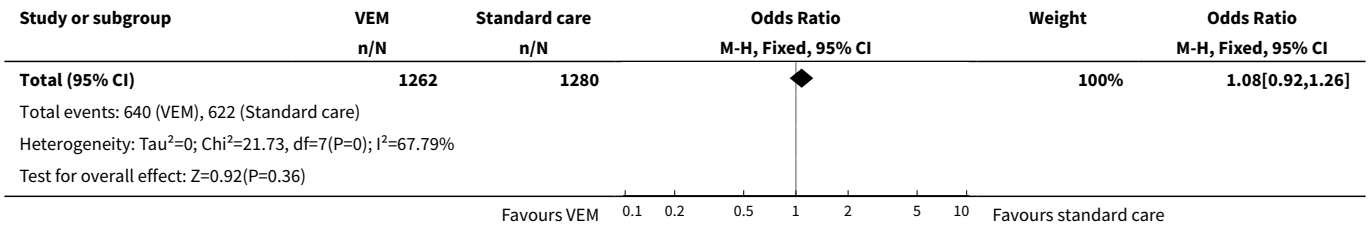
Comparison 2. Very early mobilisation versus standard care (results at 3 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or poor outcome	8	2542	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]
2 Death	8	2570	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.95, 1.70]
3 Death or dependence (modified Rankin score 3 to 6)	8	2542	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]
4 Death or institutional care	3	227	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.53, 2.07]
5 Activities of daily living (ADL) score	9	2634	Mean Difference (IV, Random, 95% CI)	0.75 [0.01, 1.49]

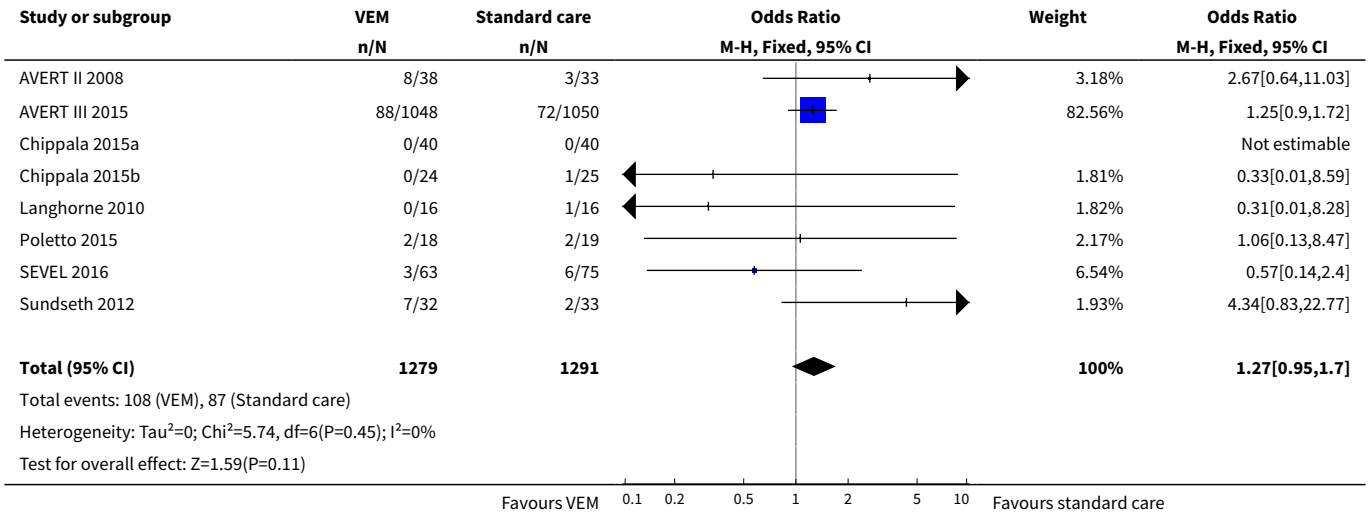
Analysis 2.1. Comparison 2 Very early mobilisation versus standard care (results at 3 months), Outcome 1 Death or poor outcome.

Study or subgroup	VEM n/N	Standard care n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
AVERT II 2008	24/38	22/33		2.88%	0.86[0.32,2.28]
AVERT III 2015	558/1038	520/1045		79.46%	1.17[0.99,1.39]
Chippala 2015a	6/40	22/40		6.2%	0.14[0.05,0.42]
Chippala 2015b	8/24	12/25		2.6%	0.54[0.17,1.72]
Langhorne 2010	4/16	9/16		2.24%	0.26[0.06,1.16]
Poletto 2015	8/16	8/17		1.29%	1.13[0.29,4.41]
SEVEL 2016	15/63	17/75		3.92%	1.07[0.48,2.36]
Sundseth 2012	17/27	12/29		1.42%	2.41[0.82,7.06]

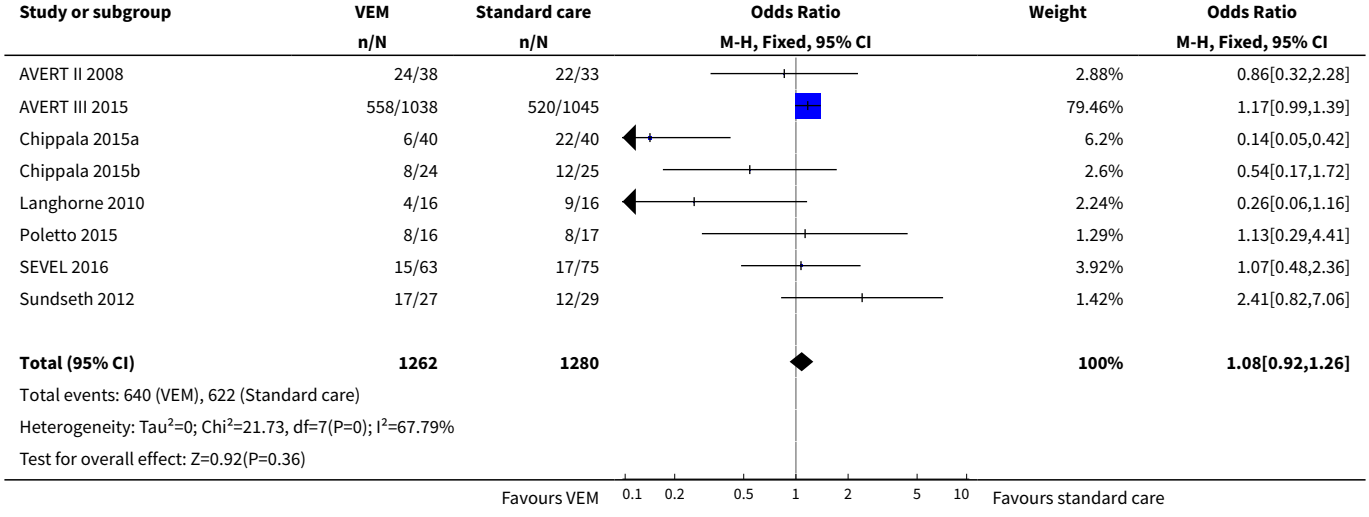




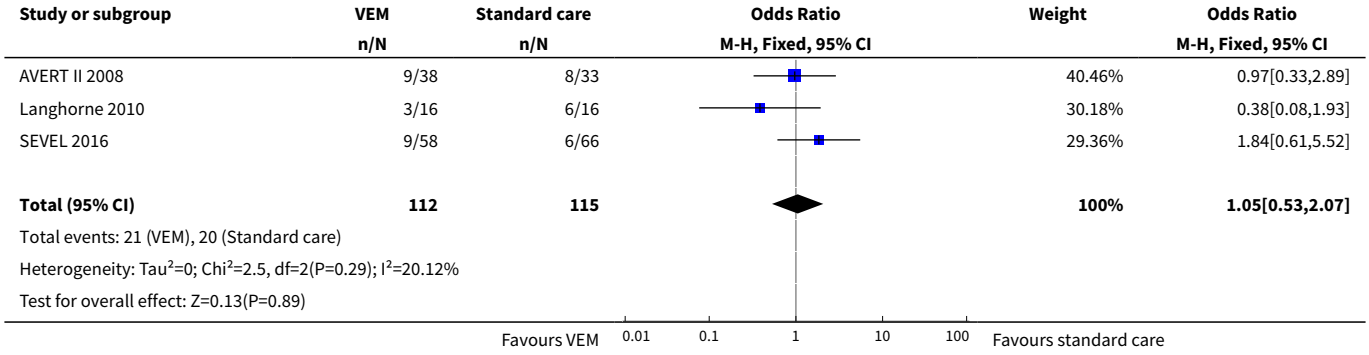
Analysis 2.2. Comparison 2 Very early mobilisation versus standard care (results at 3 months), Outcome 2 Death.



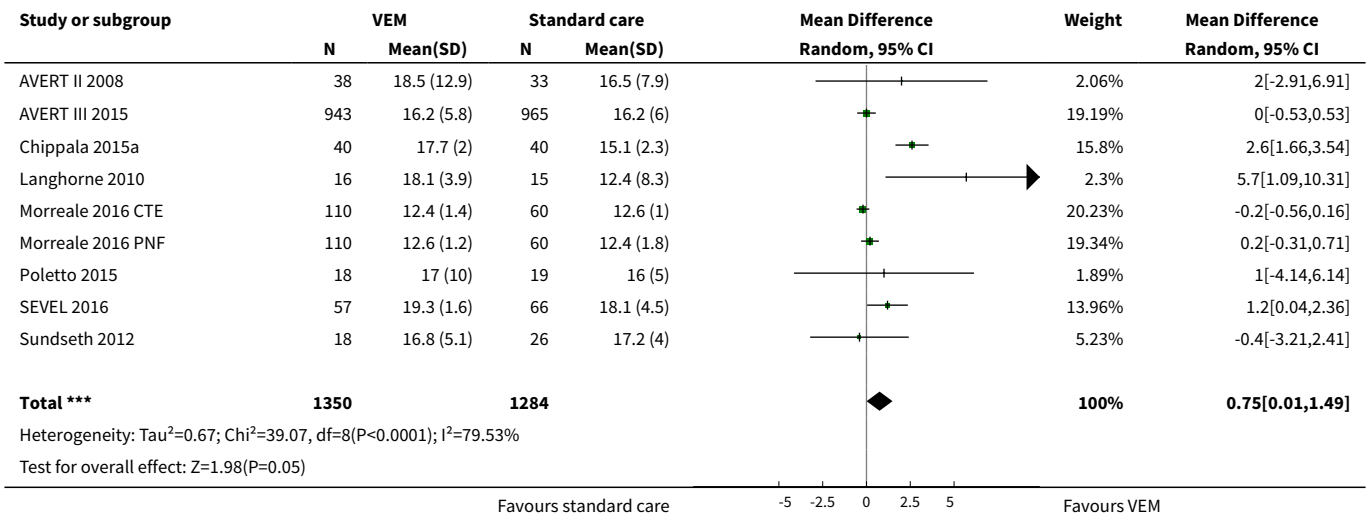
Analysis 2.3. Comparison 2 Very early mobilisation versus standard care (results at 3 months), Outcome 3 Death or dependence (modified Rankin score 3 to 6).



Analysis 2.4. Comparison 2 Very early mobilisation versus standard care (results at 3 months), Outcome 4 Death or institutional care.



Analysis 2.5. Comparison 2 Very early mobilisation versus standard care (results at 3 months), Outcome 5 Activities of daily living (ADL) score.



ADDITIONAL TABLES

Table 1. Summary of patient and treatment characteristics (included trials)

Trial	Stated aim for mobilisation activity	Participant median age (% male)	Stroke severity (moderate or severe stroke)	Early mobilisation TTFM (hours; median; IQR)	Usual care TTFM (hours; median; IQR)	Average frequency of mobilisation events per day (early vs usual care)	Average amount of mobilisation activity (early vs usual care)
AVERT II 2008	Earlier and more	75 yrs (54%)	57%	18.1 (12.8 to 21.5)	30.8 (23.0 to 39.9)	2 vs 0	167 vs 69 mins/admission mobilisation activity
AVERT III 2015	Earlier and more	73 yrs (39%)	45%	18.5 (12.8 to 22.3)	22.4 (16.5 to 29.3)	6.5 vs 3	31 vs 10 mins/day mobilisation activity
Chippala 2015a	Earlier and more	60 yrs (52%)	68%	18 (16.6 to 19.8)	30.5 (29.0 to 35.0)	Not stated	Extra 5 to 30 mins/day out-of-bed activity
Chippala 2015b	Earlier and more	64 yrs (57%)	44%	18 (16.6 to 19.8)	30.5 (29.0 to 35.0)	Not stated	Extra 5 to 30 mins/day out-of-bed activity
Langhorne 2010	Earlier and more	68 yrs (50%)	28%	27.3 (26.0 to 29.0)	32.0 (22.5 to 47.3)	Not stated	More early mobilisation, standing or walking, recorded using activity monitors (P = 0.02)
Morreale 2016	Earlier	64 yrs (72%)	< 89%	< 24	96	Not stated	60 mins/day more early mobilisation group for first 4 days
Poletto 2015	Earlier and more	65 yrs (35%)	< 70%	43	72	0.54 vs 0.03	Extra 30 mins/day out-of-bed activity
SEVEL 2016	Earlier	70 yrs (64%)	44%	25.9 (22.5 to 29.3)	71.5 (68.1 to 74.9)	Not stated	83.7 vs 56.6 mins/day
Sundseth 2012	Earlier	77 yrs (45%)	34%	13.1 (8.5 to 25.6)	33.3 (26.0 to 39.0)	Not stated	Not stated

IQR: interquartile range
mins: minutes
TTFM: time from stroke to first mobilisation activity (hours)
vs: versus
yrs: years

Table 2. Time-to-first mobilisation (TTFM) comparisons (included trials) *(Continued)*

Usual care group TTFM characteristics	Very early mobilisation group TTFM characteristics				
	12 hours	**18 hours**	**24 hours**	**> 30 hours**	**> 48 hours**
12 hours	-	-	-	-	-
18 hours	-	-	-	-	-
24 hours	-	AVERT III 2015 (2014 ppts)	-	-	-
> 30 hours	Sundseth 2012 (65 ppts)	AVEAVERT II 2008; Chippala 2015a; Chippala 2015b (211 ppts)	Langhorne 2010 (32 ppts)	-	-
> 48 hours			SEVEL 2016 167 ppts)	Poletto 2015 (39 ppts)	-

ppts = participants
Table shows Time-to-first mobilisation (TTFM) in each trial with the very early mobilisation TTFM group in the columns and usual care TTFM in the rows. The number of trials (participants) in each direct comparison of TTFM are also shown. For example Sundseth 2012 compared TTFM of approximately 12 hours with > 30 hours and included 65 participants.
We did not include data from Morreale 2016 in this analysis as we did not have access to dichotomous data on poor outcome or death.

Table 3. Inconsistency table for poor outcome (death or dependency at 3 months)

TTFM category	TTFM recorded in the trials (median; IQR)	Direct comparison (OR)	Indirect comparison (OR)	Log difference (95% CI) between direct and indirect comparisons	P value of difference between direct and indirect comparisons	Network meta-analysis (OR and 95% CI)
12 hours	13 (9 to 26)	NA	6.62	NA	NA	6.61 (1.36 to 32.09)
18 hours	18 (13 to 21)	1.17	0.80	-0.39 (-2.09 to 1.31)	0.65	1.07 (0.53 to 2.19)
24 hours	26 (22 to 29)	1.00 (reference)	Reference	Reference	Reference	Reference
> 30 hours	32 (26 to 40)	3.86	2.46	0.45 (-1.50 to 2.41)	0.65	2.74 (1.18 to 6.37)
> 48 hours	72 (68 to 75)	0.94	3.03	-1.18 (-3.33 to 0.98)	0.28	1.29 (0.50 to 3.37)

The first two columns show the TTFM category plus the actual recorded TTFM for that category.
The next two columns show the odds ratio of a poor outcome for the direct and indirect comparison of the TTFM category, with 24 hours as the reference category.
The fifth column shows the log difference, and the sixth shows the P value, between the two odds ratio estimates.
The final column shows the network meta-analysis results, which combine the direct and indirect evidence.
CI: confidence interval
IQR: interquartile range
NA: no data available
OR: odds ratio
TTFM: time-to-first mobilisation

Table 4. Inconsistency table for death at 3 months

TTFM category	TTFM recorded in the trials (median; IQR)	Direct comparison (OR)	Indirect comparison (OR)	Log difference (95% CI) between direct and indirect comparisons	P value of difference between direct and indirect comparisons	Network meta-analysis (OR and 95% CI)
12 hours	13 (9 to 26)	NA	4.18	NA	NA	4.17 (0.57 to 30.7)
18 hours	18 (13 to 21)	1.25	4.35	1.25 (-1.16 to 3.66)	0.31	1.27 (0.92 to 1.76)
24 hours	26 (22 to 29)	1.00 (reference)	-	-	-	-
> 30 hours	32 (26 to 40)	3.19	0.82	1.36 (-2.12 to 4.84)	0.44	0.96 (0.32 to 2.92)
> 48 hours	72 (68 to 75)	1.73	0.77	0.81 (-1.99 to 3.62)	0.57	1.41 (0.41 to 4.82)

The first two columns show the TTFM category plus the actual recorded TTFM for that category.
The next two columns show the odds ratio of a poor outcome for the direct and indirect comparison of the TTFM category, with 24 hours as the reference.
The fifth column shows the log difference, and the sixth shows the P value, between the two odds ratio estimates.
The final column shows the network meta-analysis results, which combine the direct and indirect evidence.
CI: confidence interval
IQR: interquartile range
NA: no data available
OR: odds ratio
TTFM: time-to-first mobilisation

Table 5. 'Summary of findings' table for network meta-analysis (NMA)

Intervention TTFM	Comparison TTFM (reference treatment)	No. of studies (participants) with direct comparison evidence	Direct comparison evidence OR (95% CI)	Quality of the evidence (GRADE) for direct comparisons	Direct plus indirect evidence (NMA) OR (95% CI)	Quality of the evidence (GRADE) for NMA
Poor outcome						
12 hours	24 hours	0	NA	NA	6.61 (1.36 to 32.1)	Low [a, b]
18 hours	24 hours	1 (2104)	1.17 (0.99 to 1.39)	Moderate [c]	1.07 (0.53 to 2.19)	Low [b, c]
30 to 48 hours	24 hours	1 (32)	3.85 (0.86 to 16.7)	Low [b, e]	2.74 (1.18 to 6.37)	Low [b, e]
More than 48 hours	24 hours	1 (167)	0.94 (0.42 to 2.08)	Low [d, e]	1.29 (0.50 to 3.37)	Low [b, e]
Death						
12 hours	24 hours	0	NA	NA	4.17 (0.57 to 30.7)	Low [a, b]
18 hours	24 hours	1 (2104)	1.25 (0.90 to 1.72)	Moderate [c]	1.27 (0.92 to 1.76)	Low [b, c]

Table 5. 'Summary of findings' table for network meta-analysis (NMA) *(Continued)*

30 to 48 hours	24 hours	1 (32)	3.03 (0.12 to 100)	Low [b, e]	0.96 (0.32 to 2.92)	Low [b, e]
More than 48 hours	24 hours	1 (167)	1.75 (0.42 to 7.14)	Low [b, e]	1.41 (0.41 to 4.82)	Low [b, e]

[a] Main trial in the loop was small and had missing data
[b] Downgraded for imprecision
[c] Based on a single large trial
[d] Based on single small trial
[e] Uncertain blinding of follow up

APPENDICES

Appendix 1. CENTRAL and DARE search strategy (the Cochrane Library)

#1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "cerebral small vessel diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"stroke, lacunar"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"]

#2 (stroke* or poststroke or apoplex* or cerebral next vasc* or brain next vasc* or cerebrovasc* or cva* or SAH):ti,ab

#3 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or "middle cerebral artery" or MCA* or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab

#4 ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal next gangli* or putaminal or putamen or "posterior fossa" or hemispher* or subarachnoid) near/5 (hemorrhag* or haemorrhage* or hematoma* or haematoma* or bleed*)):ti,ab

#5 [mh ^hemiplegia] or [mh paresis]

#6 (hemipleg* or hemipar* or paresis or paretic):ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 [mh ^"bed rest"] or [mh ^immobilization] or [mh ^rest]

#9 (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound):ti,ab

#10 ((confined or restrict* or immobili*) near/5 bed):ti,ab

#11 [mh ^"early ambulation"]

#12 [mh ^"Physical Therapy Modalities"] or [mh ^"Physical Therapy (Specialty)"]

#13 [mh ^rehabilitation] or [mh ^"activities of daily living"] or [mh ^"recovery of function"]

#14 [mh ^movement] or [mh ^locomotion] or [mh ^walking] or [mh ^"motor activity"]

#15 [mh ^"exercise movement techniques"] or [mh ^exercise] or [mh ^"exercise therapy"]

#16 (stroke unit* or "mobility protocol"):ti,ab

#17 #12 or #13 or #14 or #15 or #16

#18 [mh ^"time factors"] or [mh ^time] or early:ti,ab

#19 #17 and #18

#20 ((early or earlie* or accelerat* or immediat* or "fast-track" or timing or rapid*) near/5 (mobil* or ambulat* or rehab* or physiotherapy or "physical therapy" or "physical activity" or movement or sitting or standing or walking or semi next recumb* or "out of bed")):ti,ab

#21 #8 or #9 or #10 or #11 or #19 or #20

#22 #7 and #21

#23 [mh ^"cerebrovascular disorders" [mj]/NU,RH,TH] or [mh "basal ganglia cerebrovascular disease" [mj]/NU,RH,TH] or [mh "brain ischemia" [mj]/NU,RH,TH] or [mh "carotid artery diseases" [mj]/NU,RH,TH] or [mh "cerebral small vessel diseases" [mj]/NU,RH,TH] or [mh "intracranial arterial diseases" [mj]/NU,RH,TH] or [mh "intracranial embolism and thrombosis" [mj]/NU,RH,TH] or [mh "intracranial hemorrhages" [mj]/NU,RH,TH] or [mh ^stroke [mj]/NU,RH,TH] or [mh "brain infarction" [mj]/NU,RH,TH] or [mh "stroke, lacunar" [mj]/NU,RH,TH] or [mh ^"vasospasm, intracranial" [mj]/NU,RH,TH] or [mh ^"vertebral artery dissection" [mj]/NU,RH,TH]

#24 #18 and #23

#25 #22 or #24

Appendix 2. MEDLINE search strategy

MEDLINE 2016

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. hemiplegia/ or exp paresis/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. or/1-6

8. bed rest/ or immobilization/ or rest/

9. (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound).tw.

10. ((confined or restricted or immobili$) adj5 bed).tw.

11. early ambulation/

12. Physical Therapy Modalities/ or "Physical Therapy (Specialty)"/

13. rehabilitation/ or "activities of daily living"/ or recovery of function/

14. movement/ or locomotion/ or walking/ or motor activity/

15. exercise movement techniques/ or exercise/ or exercise therapy/

16. (stroke unit$ or mobility protocol).tw.

17. 12 or 13 or 14 or 15 or 16

18. time factors/ or time/ or early.tw.

19. 17 and 18

20. ((early or earlie$ or accelerat$ or immediat$ or fast-track or timing or rapid$) adj5 (mobil$ or ambulat$ or rehab$ or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb$ or out of bed)).tw.

21. 8 or 9 or 10 or 11 or 19 or 20

22. 7 and 21

23. *cerebrovascular disorders/nu, rh or exp *basal ganglia cerebrovascular disease/nu, rh or exp *brain ischemia/nu, rh or exp *carotid artery diseases/nu, rh or exp *cerebral small vessel diseases/nu, rh or exp *intracranial arterial diseases/nu, rh or exp *"intracranial embolism and thrombosis"/nu, rh or exp *intracranial hemorrhages/nu, rh or *stroke/nu, rh or exp *brain infarction/nu, rh or *stroke, lacunar/nu, rh or *vasospasm, intracranial/nu, rh or *vertebral artery dissection/nu, rh

24. 18 and 23

25. 22 or 24

26. Randomized Controlled Trials as Topic/

27. random allocation/

28. Controlled Clinical Trials as Topic/

29. control groups/

30. clinical trials as topic/

31. double-blind method/

32. single-blind method/

33. randomized controlled trial.pt.

34. controlled clinical trial.pt.

35. clinical trial.pt.

36. (random$ or RCT or RCTs).tw.

37. (controlled adj5 (trial$ or stud$)).tw.

38. (clinical$ adj5 trial$).tw.

39. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

40. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

41. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

42. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

43. trial.ti.

44. (assign$ or allocat$).tw.

45. controls.tw.

46. or/26-45

47. 25 and 46

48. exp animals/ not humans.sh.

49. 47 not 48

Appendix 3. Embase Ovid search strategy

1. cerebrovascular disease/ or exp basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke unit/ or stroke patient/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. paralysis/ or hemiparesis/ or hemiplegia/ or paresis/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. bed rest/ or immobilization/ or rest/

9. (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound).tw.

10. ((confined or restrict$ or immobili$) adj5 bed).tw.

11. mobilization/ or patient mobility/ or physical mobility/

12. exp physiotherapy/ or physiotherapist/ or exp rehabilitation/ or daily life activity/ or convalescence/ or "movement (physiology)"/ or exp locomotion/ or motor activity/ or exp exercise/ or exp kinesiotherapy/

13. (stroke unit$ or mobility protocol).tw.

14. 11 or 12 or 13

15. early intervention/ or time/ or early.tw.

16. 14 and 15

17. ((early or earlie$ or accelerat$ or immediat$ or fast-track or timing or rapid$) adj5 (mobil$ or ambulat$ or rehab$ or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb$ or out of bed)).tw.

18. 8 or 9 or 10 or 16 or 17

19. 7 and 18

20. *cerebrovascular disease/rh or exp *basal ganglion hemorrhage/rh or exp *brain hematoma/rh or exp *brain hemorrhage/rh or exp *brain infarction/rh or exp *brain ischemia/rh or exp *carotid artery disease/rh or *cerebral artery disease/rh or exp *cerebrovascular accident/rh or exp *intracranial aneurysm/rh or exp *occlusive cerebrovascular disease/rh

21. 15 and 20

22. 19 or 21

23. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/

24. Randomization/

25. Controlled clinical trial/ or "controlled clinical trial (topic)"/

26. control group/ or controlled study/

27. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

28. Double Blind Procedure/

29. Single Blind Procedure/ or triple blind procedure/

30. (random$ or RCT or RCTs).tw.

31. (controlled adj5 (trial$ or stud$)).tw.

32. (clinical$ adj5 trial$).tw.

33. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

34. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

35. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

36. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

37. trial.ti.

38. (assign$ or allocat$).tw.

39. controls.tw.

40. or/23-39

41. 22 and 40

42. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)

43. 41 not 42

Appendix 4. CINHAL EBSCO search strategy

S1 .(MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections")

S2 .(MH "Stroke Patients") OR (MH "Stroke Units")

S3 .TI (stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH) or AB (stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH)

S4 .TI (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) or AB (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying)

S5 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypox*)

S6 .S4 and S5

S7 .TI (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid)

S8 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)

S9 .S7 and S8

S10 .(MH "Hemiplegia")

S11 .TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)

S12 .S1 OR S2 OR S3 OR S6 OR S9 OR S10 OR S11

S13 .(MH "Early Ambulation")

S14 .(MH "Bed Rest") OR (MH "Bed Rest Care (Iowa NIC)") OR (MH "Rest (Iowa NOC)")

S15 .(MH "Immobilization")

S16 .TI (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound) OR AB (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound)

S17 .TI ((confined or restricted or immobili*) N5 bed) OR AB ((confined or restricted or immobili*) N5 bed)

S18 .(MH "Physical Mobility") OR (MH "Mobility Therapy (Saba CCC)")

S19 .(MH "Ambulation Aids+") OR (MH "Ambulation Therapy (Saba CCC)") OR (MH "Exercise Therapy: Ambulation (Iowa NIC)") OR (MH "Ambulation: Walking (Iowa NOC)") OR (MH "Walking+")

S20 .(MH "Activities of Daily Living+") or (MH "Physical Therapy+") or (MH "Rehabilitation") or (MH "Movement+")

S21 .TI (stroke unit* or mobility protocol) OR AB (stroke unit* or mobility protocol)

S22 .S18 OR S19 OR S20 OR S21

S23 .(MH "Time+") OR (MH "Early Intervention") OR TI (early) OR AB (early)

S24 .S22 AND S23

S25 .TI ((early or earlie* or accelerat* or immediate* or fast-track or timing or rapid) N10 (mobil* or ambulat* or rehab* or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb* or out of bed)) OR AB ((early or earlie* or accelerat* or immediate or fast-track or timing or rapid) N10 (mobil* or ambulat* or rehab* or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb* or out of bed))

S26 .S13 OR S14 OR S15 OR S16 OR S17 OR S24 OR S25

S27 .S12 AND S26

S28 .(MH "Randomized Controlled Trials") or (MH "Random Assignment") or (MH "Random Sample+")

S29 .(MH "Clinical Trials") or (MH "Intervention Trials") or (MH "Therapeutic Trials")

S30 .(MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies")

S31 .(MH "Control (Research)") or (MH "Control Group")

S32 .(MH "Quasi-Experimental Studies")

S33 .PT (clinical trial or randomized controlled trial)

S34 .TI (random* or RCT or RCTs) or AB (random* or RCT or RCTs)

S35 .TI (controlled N5 (trial* or stud*)) or AB (controlled N5 (trial* or stud*))

S36 .TI (clinical* N5 trial*) or AB (clinical* N5 trial*)

S37 .TI ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*)) or AB ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*))

S38 .TI ((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*)) or AB ((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*))

S39 .TI ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*)) or AB ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*))

S40 .TI trial

S41 .TI (assign* or allocat*) or AB (assign* or allocat*)

S42 .TI controls or AB controls

S43 .TI (quasi-random* or quasi random* or pseudo-random* or pseudo random*) or AB (quasi-random* or quasi random* or pseudo-random* or pseudo random*)

S44 .S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43

S45 .S27 AND S44

Appendix 5. PsycINFO Ovid search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebral small vessel disease/ or cerebrovascular accidents/ or subarachnoid hemorrhage/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

5. hemiparesis/ or hemiplegia/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. or/1-6

8. (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound).tw.

9. ((confined or restricted or immobili$) adj5 bed).tw.

10. physical mobility/ or physical therapy/ or physical activity/ or physical therapists/

11. rehabilitation/ or "activities of daily living"/

12. motor processes/ or locomotion/ or walking/

13. exercise/

14. (stroke unit$ or mobility protocol).tw.

15. 10 or 11 or 12 or 13 or 14

16. early intervention/ or time/ or early.tw.

17. 15 and 16

18. ((early or earlie$ or accelerat$ or immediat$ or fast-track or timing or rapid$) adj5 (mobil$ or ambulat$ or rehab$ or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb$ or out of bed)).tw.

19. 8 or 9 or 17 or 18

20. 7 and 19

21. clinical trials/ or treatment effectiveness evaluation/ or placebo/

22. (random$ or RCT or RCTs).tw.

23. (controlled adj5 (trial$ or stud$)).tw.

24. (clinical$ adj5 trial$).tw.

25. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

26. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

27. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

28. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

29. trial.ti.

30. (assign$ or allocat$).tw.

31. controls.tw.

32. or/21-31

33. 20 and 32

Appendix 6. AMED Ovid search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/ or stroke/

2. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch? emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h? ematoma$ or bleed$)).tw.

5. hemiplegia/ or gait disorders/

6. (hemipleg$ or hemipar$ or paresis or paretic).tw.

7. 1 or 2 or 3 or 4 or 5 or 6

8. bed rest/ or immobilization/ or rest/

9. (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound).tw.

10. ((confined or restricted or immobili$) adj5 bed).tw.

11. mobilisation/

12. physical therapy modalities/ or physiotherapists/ or exp exercise therapy/ or rehabilitation/ or exp locomotion/ or movement/ or motor activity/ or "activities of daily living"/

13. (stroke unit$ or mobility protocol).tw.

14. 11 or 12 or 13

15. time/ or early.tw.

16. 14 and 15

17. ((early or earlie$ or accelerat$ or immediat$ or fast-track or timing or rapid$) adj5 (mobil$ or ambulat$ or rehab$ or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb$ or out of bed)).tw.

18. 8 or 9 or 10 or 16 or 17

19. 7 and 18

20. clinical trials/ or randomized controlled trials/ or random allocation/

21. research design/ or comparative study/

22. double blind method/ or single blind method/

23. (random$ or RCT or RCTs).tw.

24. (controlled adj5 (trial$ or stud$)).tw.

25. (clinical$ adj5 trial$).tw.

26. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

27. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

28. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

29. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

30. trial.ti.

31. (assign$ or allocat$).tw.

32. controls.tw.

33. or/20-32

34. 19 and 33

Appendix 7. SPORTDiscus EBSCO search strategy

S1 .DE "CEREBROVASCULAR disease" OR DE "BRAIN -- Hemorrhage" OR DE "CEREBRAL embolism & thrombosis" OR DE "STROKE" OR DE "BRAIN -- Wounds & injuries" OR DE "BRAIN damage"

S2 .DE "CEREBROVASCULAR disease -- Patients"

S3 .TI (stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH) or AB (stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH)

S4 .TI (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) or AB (brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying)

S5 .TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypox*)

S6 .S4 and S5

S7 .TI (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid)

S8 .TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)

S9 .S7 and S8

S10 .DE "HEMIPLEGIA" OR DE "HEMIPLEGICS" OR DE "GAIT disorders"

S11 .TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)

S12 .S1 OR S2 OR S3 OR S6 OR S9 OR S10 OR S11

S13 .DE "REST" OR DE "IMMOBILIZATION (Therapeutics)"

S14 .TI (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound) OR AB (bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound)

S15 .TI ((confined or restricted or immobili*) N5 bed) OR AB ((confined or restricted or immobili*) N5 bed)

S16 .DE "PHYSICAL activity” OR DE "PHYSICAL therapists"

S17 .DE "REHABILITATION" OR DE "MEDICAL rehabilitation" OR DE "RECOVERY training" OR DE "MOVEMENT therapy"

S18 .DE "ACTIVITIES of daily living training" OR DE "ACTIVITIES of daily living" OR DE "FUNCTIONAL training"

S19 .DE "BODY movement" OR DE "MOVEMENT therapy" OR DE "LOCOMOTION" OR DE "WALKING" OR DE "EXERCISE" OR DE "ARM exercises" OR DE "CHAIR exercises" OR DE "LEG exercises" OR DE "STRENGTH training" OR DE "STRETCHING exercises"

S20 .DE "EXERCISE therapy"

S21 .TI (stroke unit* or mobility protocol) OR AB (stroke unit* or mobility protocol)

S22 .S16 OR S17 OR S18 OR S19 OR S20 OR S21

S23 .TI (early) OR AB (early)

S24 .S22 AND S23

S25 .TI ((early or earlie* or accelerat* or immediat* or fast-track or timing or rapid) N10 (mobil* or ambulat* or rehab* or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb* or out of bed)) OR AB ((early or earlie* or accelerat* or immediate or fast-track or timing or rapid) N10 (mobil* or ambulat* or rehab* or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb* or out of bed))

S26 .S13 OR S14 OR S15 OR S24 OR S25

S27 .S12 AND S26

Appendix 8. Web of Science search strategy

Web of Science: Core Collection 1900-2016 (Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), and Arts & Humanities Citation Index (A&HCI)).

26. #25 AND #12 AND #6 (Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=2006-2016)

25. #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13

24. TS=controls

23. TS=(assign* or allocat*)

22. TI=trial

21. TS=(placebo* or sham)

20. TS=(cross-over or cross over or crossover)

19 .TS=((singl* or doubl* or tripl* or trebl*) NEAR/5 (blind* or mask*))

18. TS=((control or experiment* or conservative) NEAR/5 (treatment or therapy or procedure or manage*))

17. TS=(quasi-random* or quasi random* or pseudo-random* or pseudo random*)

16. TS=((control or treatment or experiment* or intervention) NEAR/5 (group* or subject* or patient*))

15. TS=(clinical* NEAR/5 trial*)

14. TS=(controlled NEAR/5 (trial* or stud*))

13. TS=(random* or RCT or RCTs)

12. #7 OR #8 OR #11

11. #9 AND #10

10. TS=(mobil* or ambulat* or rehab* or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb* or out of bed)

9. TS=(early or earlie* or accelerat* or immediat* or fast-track or timing or rapid*)

8. TS=((confined or restricted or immobili*) NEAR/5 bed).

7. TS=(bed rest or bed-rest or bedrest or bed bound or bed-bound or bedbound).

6. #5 OR #4 OR #3 OR #2 OR #1

5. TS=((unilateral or spatial or hemi$spatial or visual) NEAR/5 neglect)

4. TS=(hemipleg* or hemipar* or paresis or paretic or hemineglect or hemi-neglect)

3. TS=((brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) NEAR/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*))

2. TS=((brain* or cerebr* or cerebell* or intracran* or intracerebral) NEAR/5 (isch$emi* or infarct* or thrombo* or emboli* or occlus*))

1. TS=(stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc* or cva* or apoplex* or SAH)

WHAT'S NEW

Date	Event	Description
14 March 2018	New search has been performed	Updated literature search with no new completed trials identified. The review now includes nine RCTs (2958 participants). Text revised and exploratory network meta-analysis added.
14 March 2018	New citation required but conclusions have not changed	No change to the conclusions.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 1, 2009

Date	Event	Description
5 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For this review update, Peter Langhorne co-ordinated the updated searches, drafted the update, and re-drafted in response to comments. Peter Langhorne and Trish Bate extracted references. Julie Bernhardt, Janice Collier, Matthew Thuy, and Trish Bate refined the manuscript.

For the original review, Julie Bernhardt drafted the protocol and participated in all stages of the review. Janice Collier and Lynn Legg refined the protocol and contributed to the planned bibliographic searches. Matthew Thuy and Lynn Legg identified studies, assessed methodological quality, and checked the extracted data. Matthew Thuy performed much of the planned bibliographic searches, obtained full-text articles and made contact with study authors. All review authors commented on drafts of the manuscript.

DECLARATIONS OF INTEREST

Several of the review authors were trialists in at least one of the included trials. However, we allocated trial selection decisions in a manner that avoided trialists making decisions about their own trials.

Peter Langhorne: PL is trialist in two of the included trials (AVERT III 2015; Langhorne 2010). However, trial selection decisions were allocated in a manner to avoid making decisions about his own trials.
Janice M Collier: JC is trialist in two of the included trials (AVERT II 2008; AVERT III 2015). However, trial selection decisions were allocated in a manner to avoid making decisions about her own trials.
Patricia J Bate: none known
Matthew NT Thuy: none known
Julie Bernhardt: JB is trialists in three of the included trials (AVERT II 2008; AVERT III 2015; Langhorne 2010). However, trial selection decisions were allocated in a manner to avoid making decisions about her own trials.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Priority Review Support Programme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added, or more explicitly defined, the following secondary outcomes:

- Death or requiring institutional care: we defined institutional care as care within a residential home, nursing home, or hospital at follow-up.
- Type of complication (adverse events): categorised as complications of immobility (deep vein thrombosis (DVT), pulmonary embolism (PE), incidence and grade of pressure sores (using standardized grading scale), chest infection, urinary tract infection, falls), and other complications.
- 'Time to walking unassisted (without help from another person) reported alone or as a component of a functional mobility scale' has been replaced by 'Able to walk (Outcome 1.8) and mobility score (Outcome 1.9)'. This minor change was to allow the inclusion of more trial data.
- 'Length of acute stay in acute hospital (Outcome 1.13)' was added to provide an indicator of resource use.

Search Strategy: the WHO Registry now incorporates the Australian Clinical Trials Registry (ACTR; now the Australian New Zealand Clinical Trials Registry (ANZCTR)), the Netherlands Trial Register, and ISRCTNs data sets.

Network meta-analysis: we included an exploratory network meta-analysis in view of the diversity of the included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Early Ambulation [adverse effects] [mortality]; *Stroke Rehabilitation [mortality]; Activities of Daily Living; Length of Stay; Network Meta-Analysis; Quality of Life; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Humans