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Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT)

OPEN

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ABSTRACT

Objective: Our prespecified dose-response analyses of A Very Early Rehabilitation Trial (AVERT) aim to provide practical guidance for clinicians on the timing, frequency, and amount of mobilization following acute stroke.

Methods: Eligible patients were aged ≥18 years, had confirmed first (or recurrent) stroke, and were admitted to a stroke unit within 24 hours of stroke onset. Patients were randomized to receive very early and frequent mobilization, commencing within 24 hours, or usual care. We used regression analyses and Classification and Regression Trees (CART) to investigate the effect of timing and dose of mobilization on efficacy and safety outcomes, irrespective of assigned treatment group.

Results: A total of 2,104 patients were enrolled, of whom 2,083 (99.0%) were followed up at 3 months. We found a consistent pattern of improved odds of favorable outcome in efficacy and safety outcomes with increased daily frequency of out-of-bed sessions (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.09 to 1.18, $p < 0.001$), keeping time to first mobilization and mobilization amount constant. Increased amount (minutes per day) of mobilization reduced the odds of a good outcome (OR 0.94, 95% CI 0.91 to 0.97, $p < 0.001$). Session frequency was the most important variable in the CART analysis, after prognostic variables age and baseline stroke severity.

Conclusion: These data suggest that shorter, more frequent mobilization early after acute stroke is associated with greater odds of favorable outcome at 3 months when controlling for age and stroke severity.

Classification of evidence: This study provides Class III evidence that shorter, more frequent early mobilization improves the chance of regaining independence after stroke. *Neurology*® 2016;86:2138–2145

GLOSSARY

AVERT = A Very Early Rehabilitation Trial; **CART** = Classification and Regression Tree; **CI** = confidence interval; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **ROC** = receiver operating characteristic; **rtPA** = recombinant tissue plasminogen activator; **SAE** = serious adverse event; **TTFM** = time from stroke onset to first mobilization out of bed; **VEM** = very early mobilization.

In our primary intention-to-treat analysis for A Very Early Rehabilitation Trial (AVERT), we reported that patients randomized to usual care had greater odds of a favorable outcome (modified Rankin Scale [mRS] score 0–2) at 3 months compared to those receiving the very early mobilization (VEM) protocol.[1] However, a recommendation of "usual care" is of limited value to clinicians seeking guidance, as usual care was not standardized and mobilization often commenced within 24 hours of stroke. Importantly, "early" does not encapsulate all aspects of the interventions delivered in this trial. The VEM protocol was earlier, more frequent, and higher amounts of out-of-bed activity,[2] a "complex intervention,"[3] which was consistent with practices

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Supplemental data at Neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by the authors.

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associated with better outcome in Norway.[4] Greater amounts of physical training post-stroke is associated with improved outcomes (without harm) in a number of meta-analyses,[5,6] and many guidelines recommend increasing training dose. Increased frequency, a critical intervention characteristic, was supported by 2 lines of evidence. Exercise benefits in sedentary adults, accumulated in multiple, short bouts, appear equivalent to a single, longer bout,[7,8] and bursts of training appear highly suited to acute stroke patients. Further, frequent repetition of training (distributed practice) is associated with improved motor learning after stroke.[9,10] In AVERT, all interventions were carefully recorded, thus allowing a detailed investigation of dose response. Our aim for these prespecified dose-response analyses[11] is to provide practical guidance for clinicians.

The trial is registered with the Australia and New Zealand Clinical Trial Registry (ACTRN12606000185561).

METHODS Detailed methods are described elsewhere.[1,11] In brief, AVERT, conducted in 56 stroke units in 5 countries, is a pragmatic, parallel-group, randomized controlled trial. Patients with ischemic or hemorrhagic stroke, admitted within 24 hours of onset, were eligible. Patients with early deterioration, another serious illness, unstable coronary conditions, not rousable to voice, or failing physiologic screening criteria were excluded. Patients or their nominated representative provided written consent. Randomization was blocked, balanced by site, and stratified by stroke severity. All trial personnel were masked to group, except the intervention monitor.

Standard protocol approvals, registrations, and patient consents. Ethical approval was obtained from relevant site institutional boards.

Procedures. Patients were randomized to receive either usual care or frequent out-of-bed activity (mobilization) in addition to usual care (VEM).[1,11] VEM patients commenced mobilization within 24 hours of stroke and trained physiotherapy and nursing staff helped them continue task-specific out-of-bed activity, targeting recovery of active sitting, standing, and walking activity, at a frequency and intensity (amount) guided by an intervention protocol. Functional ability at baseline, monitored daily and adjusted with recovery, guided the intervention dose with 4 titrations specified. For example, in low arousal, dependent patients (level 1), active sitting with assistance was the mobilization target, with each session lasting a minimum of 10 and maximum of 30 minutes. With higher-functioning patients (level 4), standing and walking were likely targets, each session again lasting a minimum of 10 minutes with no restricted maximum (patient-dependent). The frequency of sessions per day also varied according to functional level. Importantly, passive sitting (resting in a chair) was not classified as a VEM mobilization activity and sitting for more than 50 minutes at one time was discouraged. Intervention lasted 14 days or until discharge, whichever was sooner. Physiotherapists and nurses, with separate intervention targets, worked together to deliver the intervention dose. All mobilization activities were recorded online.

Outcome measures. Our primary outcome was a favorable outcome on the modified Rankin Scale (mRS 0–2) at 3 months poststroke.[1] Secondary outcomes were time (days) to achieve unassisted walking over 50 meters, the proportion of patients achieving unassisted walking by 3 months, death, and the number of serious adverse events (SAEs) at 3 months. Immobility-related SAEs (deep venous thrombosis, pulmonary emboli, pressure sores, chest infections, urinary tract infections) and neurologic SAEs (stroke progression, recurrent stroke) were examined separately.

Dose measures. The dose-response analyses examine the 3 main characteristics of dose: (1) time from stroke onset to first mobilization out of bed (TTFM, hours), (2) median number of out-of-bed sessions per patient per day (frequency), and (3) median minutes of out-of-bed activity per patient per day (daily amount). Total minutes of out-of-bed activity over the intervention period (total amount) accounts for varying lengths of hospital stay.

Nurses recorded type of activity and time of the day each activity began, but not minutes, as this was not routine practice. Physiotherapists recorded activity type, time the activity began, and total out-of-bed activity time (minutes), consistent with their routine practice. Consequently, daily amount (minutes) and total amount (minutes) of out-of-bed activity reflect physiotherapy data alone, while TTFM and frequency of mobilizations is derived from both nurse and physiotherapist data. Episodes of sitting, standing, or walking activity separated from another episode of activity by >5 minutes of rest (e.g., in a chair) constituted 2 separate mobilizations. Active time (minutes), e.g., practicing sit-to-stand from the chair, was recorded by the physiotherapist.

Statistical analysis. These dose-response analyses repeat our major primary and secondary analyses[1] with dose characteristics (TTFM, frequency, daily amount, total amount) as independent variables, and were prespecified in our statistical analysis plan.[11] To avoid excessive collinearity between daily amount and total amount, we tested 2 separate models, adjusted for age and baseline stroke severity (NIH Stroke Scale [NIHSS]), for all analyses, as follows:

1. Model 1: TTFM, median daily number of out-of-bed sessions (frequency), median daily out-of-bed session time (in 5-minute increments).
2. Model 2: TTFM, median daily number of out-of-bed sessions (frequency), total minutes in out-of-bed activity over the intervention period (in 5-minute increments).

The primary analysis, with favorable outcome (mRS 0–2) at 3 months as the dependent variable, was conducted using binary logistic regression models.

The dose effect on the odds of achieving unassisted walking by 3 months was investigated using binary logistic regression analyses (effect sizes: adjusted odds ratios [ORs] and 95% confidence intervals [CIs]) while the time (days) to achieve unassisted walking (censored at 3 months) was assessed using Cox regression analyses (adjusted hazard ratios with 95% CIs).

We analyzed mortality outcomes using binary logistic regression with death at 3 months (mRS 6) as the dependent variable (effect sizes: adjusted ORs with 95% CIs). We investigated dose effect on counts of SAEs using negative binomial regression

(effect sizes: adjusted incidence rate ratios with 95% CIs). Immobility-related and neurologic SAEs were analyzed separately.

We used Classification and Regression Tree (CART) advanced analysis (Salford Predictive Modeler Software Suite version 7, Salford Systems, San Diego, CA) to further investigate the complex interactions between patient and dose characteristics and favorable outcome. CART is a binary partitioning statistical method that starts with the total sample and, in a stepwise manner, splits the sample into subsamples that are homogenous with respect to a defined outcome.[12] The input variable that achieves the most effective split is dichotomized by automated analysis at an optimal threshold, maximizing the homogeneity within, and separation between, resulting subgroups. To maximize model performance (assessed by area under the receiver operating characteristic [ROC] curve), a 10-fold internal cross-validation, where data are randomly divided into 10 groups with 9 used to build the model (training) and 1 used to validate (testing), is performed. In addition to the classification tree, CART numerically ranks each input used to build the tree by relative importance.

Our CART1 (figure 1) analysis included all prespecified subgroup variables[1] (age, NIHSS, stroke type, recombinant tissue plasminogen activator [rtPA] treatment), group allocation, and the 3 dose characteristics (TTFM, frequency, and daily amount). We explored the relative importance of each variable to achieving a favorable outcome (mRS 0–2). CART2 (figure e-1 on the *Neurology*® Web site at Neurology.org) was used to investigate multidimensional relationships between dose characteristics alone and favorable outcome.

RESULTS Between July 18, 2006, and October 16, 2014, we randomly assigned 2,104 patients to VEM (n = 1,054) and usual care (n = 1,050), with 2,083 (99%) patients followed to the primary 3-month endpoint. This group constitutes the dataset for all analyses in this article. In total, 25% were over 80 years of age, few were disabled prior to stroke, more than 43% of patients experienced a moderate to severe stroke (NIHSS > 7), and 12% were diagnosed with intracerebral hemorrhage (table 1). A total of 1,584 patients (75%) had no disability (premorbid mRS 0) prior to stroke, a further 519 (24%) had slight disability (mRS 1–2), and 1,833 (87%) could walk without aids. The median (interquartile range [IQR]) time to first mobilization was 20.2 hours (14.7–23.8), while 1,588 (75%) participants commenced out-of-bed activity within 24 hours of stroke (table 2).

Greater TTFM was associated with a reduced odds of favorable outcome (0.99, 0.98–1.00, $p = 0.036$; table 3). In model 1 (favorable outcome), the effect of TTFM was adjusted for median daily number of sessions (frequency), median daily minutes (daily amount), age, and baseline NIHSS. In this example, the significant effect for TTFM on the odds of a favorable outcome should be interpreted as follows: for 2 patients of similar age and stroke severity, receiving a similar frequency and daily amount of out-of-bed activity, the patient who starts mobilization earlier has improved odds of a favorable outcome.

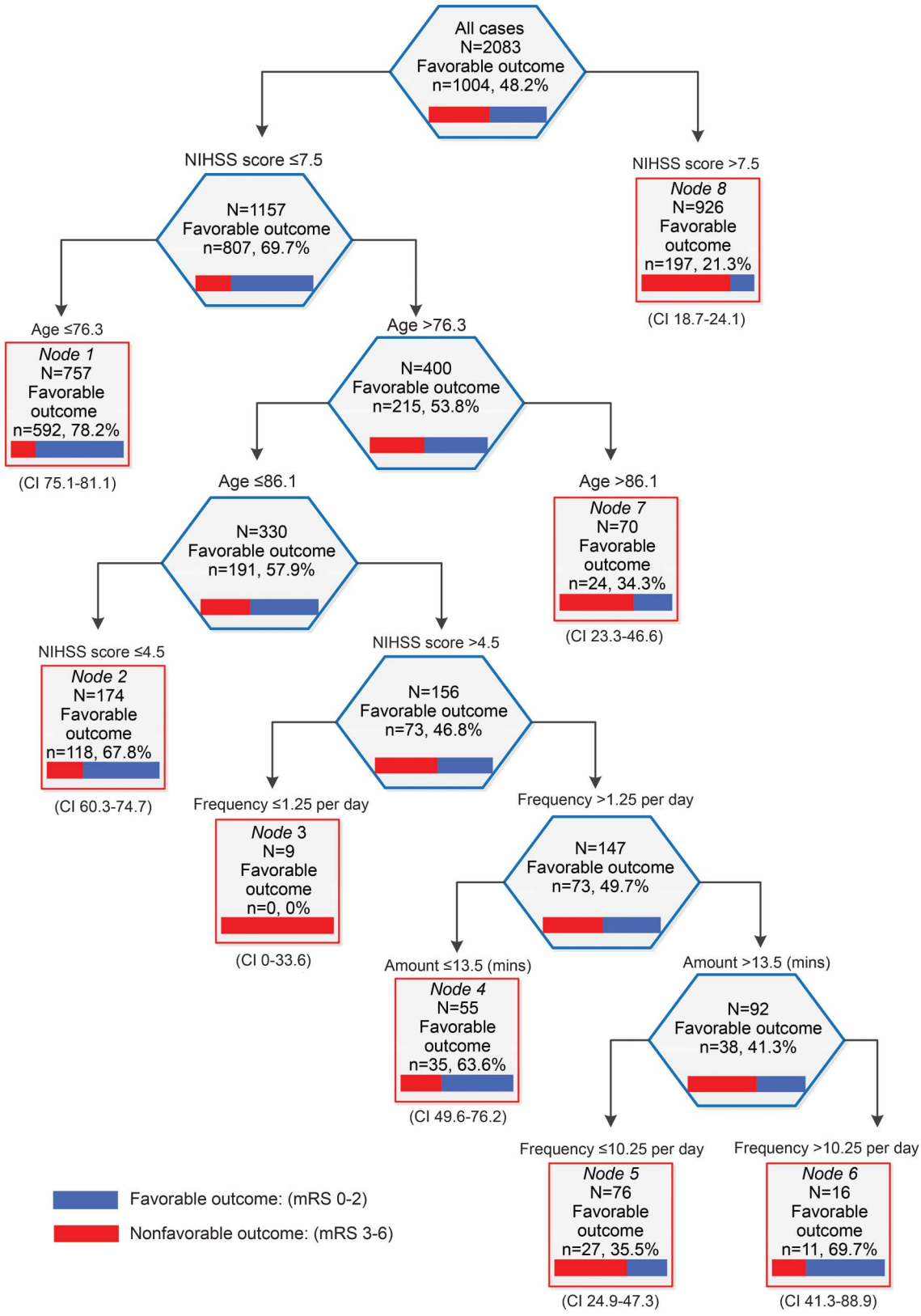
For efficacy outcomes, favorable outcome (mRS 0–2) and walking by 3 months, we found a similar pattern of association with each of the dose characteristics, and all associations were significant (table 3). In model 1, TTFM, frequency, and daily amount all significantly influenced the odds of a favorable outcome. Keeping TTFM and frequency constant, every extra 5 minutes of out-of-bed activity per day reduced the odds of a favorable outcome. Increasing the frequency of sessions improved the odds of favorable outcome by 13% (95% CI 9–18 $p < 0.001$) and improved the odds of walking 50 meters unassisted by 66% (95% CI 53–80, $p < 0.001$) when TTFM and daily amount were kept constant. This pattern was similar in model 2.

When examining associations with intervention characteristics and death, increasing session frequency was the only characteristic that reduced the odds of death by approximately 20% (table 4). Nonfatal SAEs showed less consistent associations between dose characteristics and outcome. TTFM was not significant in any model, but frequency and amount were (table 4). Given the relatively few immobility and neurologic SAEs, these results should be viewed with caution.

In CART1 (figure 1), including TTFM, frequency and daily amount, age, NIHSS, stroke subtype, rtPA treatment, and randomization group, we found good to excellent performance, with a training ROC of 0.78 and a testing ROC of 0.77. The relative contribution of variables to the model showed initial stroke severity (NIHSS), a known predictor of recovery, was most important (100%), followed by session frequency (39.2%), age (32.4%), TTFM (10.5%), and daily amount (2.7%). Treatment group was not an important discriminator.

Younger patients (≤76.3 years) and those with low NIHSS score (≤7.5) had high probability of a favorable outcome (78.2%). Those with NIHSS score >7.5 showed low (21.3%) probability of achieving little to no disability (mRS 0–2). The influence of intervention characteristics becomes evident as we move farther down the tree. For example, at terminal node 4 (figure 1), patients between 76.3 and 86.1 years, with an NIHSS score >4.5 (but ≤7.5), showed greater probability of a favorable outcome (63.6%) if they received no more than 13.5 minutes per day distributed across frequent (short) sessions. Frequency again split the tree for terminal nodes 5 and 6, indicating that more frequent sessions to achieve a higher dose (>13.5 minutes per day) was associated with greater odds of a good outcome. CART2 (figure e-1) explores the influence of dose variables on outcome. Further exploration of CART1 large terminal nodes 1 (younger age) and 8 (more severe stroke) are shown in figures e-2 and e-3. TTFM, frequency, amount, and group are all influential splitters in these models.

Figure 1 Classification and Regression Tree (CART) advanced analysis investigating interactions between dose and patient characteristics and odds of a favorable outcome (modified Rankin Scale [mRS] 0–2)



Time to first mobilization, median daily number of out-of-bed sessions per day (frequency), median daily out-of-bed activity session time (amount), age (in years), and stroke severity (NIH Stroke Scale [NIHSS]). Frequency is derived from nursing and physiotherapist data. Amount (minutes) is derived from physiotherapist data only. CI = confidence interval.

Table 1 Baseline characteristics of all patients

	All patients (n = 2,104)
Recruitment region, n (%)	
Australia/New Zealand	1,243 (59)
Asia	251 (12)
United Kingdom	610 (29)
Patient details	
Age, y, median (IQR)	72.5 (62.9–80.3)
Female	818 (40)
Risk factors, n (%)	
Hypertension	1,424 (68)
Ischemic heart disease	487 (23)
Hypercholesterolemia	929 (40)
Diabetes mellitus	467 (22)
Atrial fibrillation	466 (22)
Smoking, n (%)	
Never smoked	945 (45)
Smoker[a]	431 (20)
Ex-smoker[b]	693 (33)
Unknown	35 (2)
Living arrangement at time of admission	
Home alone/with someone, n (%)	532 (25)/1,542 (73)
Time (in hours) to randomization, median (IQR)	18.2 (12.3–21.8)
First stroke, n (%)	1,721 (82)
NIHSS score	
Median (IQR)	7 (4–12)
Mild (NIHSS 1–7), n (%)	1,170 (56)
Moderate (NIHSS 8–16), n (%)	643 (31)
Severe (NIHSS > 16), n (%)	291 (14)
Stroke type (Oxfordshire Stroke Classification), n (%)	
TACI	456 (22)
PACI	668 (32)
POCI	199 (9)
LACI	523 (25)
ICH	258 (12)
Treated with rtPA	507 (24)
Baseline walking (MSAS), n (%)	
Independent	855 (41)
Supervised or assisted	1,060 (50)

Abbreviations: ICH = intracerebral hemorrhage; IQR = interquartile range; LACI = lacunar infarct; mRS = modified Rankin Scale; MSAS = Mobility Scale for Acute Stroke[13] walking score; NIHSS = NIH Stroke Scale; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; rtPA = recombinant tissue plasminogen activator; TACI = total anterior circulation infarct.
[a] Current smoker, or quitting in the last 2 years.
[b] Quitting >2 years ago.

DISCUSSION We found a consistent pattern of association between the odds of experiencing little or no disability (mRS 0–2) at 3 months and the intervention characteristics irrespective of treatment group. In particular, we saw 13% improvement in the odds of a favorable outcome with each additional session of out-of-bed activity per day (keeping the time to first mobilization and daily amount constant). Conversely, increasing the amount of time spent in out-of-bed activity, keeping the frequency and time to first mobilization constant, reduced the odds of a favorable outcome. The potentially beneficial effect of increasing the frequency of out-of-bed activity (but not the amount) was consistent across most of the efficacy and safety analyses.

These findings begin to unpack the primary results, where we reported that VEM (very early, frequent, and higher-dose out-of-bed activity) reduced the odds of a favorable outcome at 3 months.[1] This dose-response analysis suggests that increased frequency of mobilization (keeping other intervention characteristics constant) helps reduce disability and increases the odds of walking by 3 months and reduces the odds of death. However, increasing the minutes of out-of-bed activity was more likely to result in worse outcomes. In other words, these findings indicate that short, frequent sessions may be preferable for many patients in the first weeks after stroke.

Addition of the CART analyses provided further support for the important influence of session frequency on outcome. Even with the inclusion of patient characteristics considered strongly predictive of outcome after stroke (such as stroke severity and age), intervention characteristics played an explicit and important role, defining homogenous groups of patients based on their chances of achieving the favorable outcome. Indeed, in patients with more severe stroke (NIHSS > 13.5), a more favorable outcome was evident in those with more rather than less sessions (figure e-3). In humans and animals, there is limited discussion about the potential effect of frequency of intervention on stroke outcome. Recently, Bell et al.[14] studied skilled reaching in stroke-affected mice and found that twice daily, higher-dose training accelerated recovery and improved final outcome compared to a once-a-day, lower-dose regimen. In humans, a number of systematic reviews and meta-analyses suggest a dose-response relationship, with more intensive therapy resulting in improved functional outcome after stroke.[5,6,15] Definitions for therapy intensity vary, but to date the focus has been on amount (minutes) rather than frequency (repetitions of a task, or sessions per day).[16] Generally, inadequate reporting of therapy interventions, together with significant heterogeneity in the timing, amount, frequency, and intensity of training provided, complicates messaging of poststroke therapy, particularly in the first few weeks, where few studies exist.[17]

Table 2 Intervention summary, all patients

Characteristics	All patients (n = 2,104), median (IQR)
Time to first mobilization, h	20.2 (14.7–23.8); n = 2,078; missing[a] = 26
Frequency per person[b] (median daily sessions of out-of-bed activity)	5 (3–8)
Daily amount per person[c] (median minutes per day spent in out-of-bed activity)	17.5 (6–35)
Total amount per person[c] (minutes over the intervention period[d])	120 (50–235)

Abbreviation: IQR = interquartile range.
Median estimates include days when time or number of out-of-bed sessions = 0; i.e., the patient was recorded as not getting up on that day.
[a] Missing: Hours to first mobilization (n = 26); these patients were never mobilized, due to an early serious adverse event (n = 13), decision to palliate (n = 5), or early death (n = 5), transfer from the stroke unit (n = 1), or drop-out (n = 1). For these patients, therapy and nurse recording forms were completed throughout their stroke unit stay, with zero time and zero sessions.
[b] Frequency is derived from nursing and physiotherapist data.
[c] Amount (minutes) is derived from physiotherapist data only.
[d] Total amount of out-of-bed activity over the intervention period was estimated over the total length of stay or until 14 days poststroke (whichever occurred first).

Interestingly, a 3-arm early rehabilitation trial testing upper limb constraint regimens, although small (n = 52), also found that a higher amount of training was inferior to lower-dose usual care.[18] A critical challenge in rehabilitation is determining who should be targeted and when and what is the optimal intervention.[19]

The influence of time to first mobilization was less clear, partly due to a compact distribution pattern with the median time (IQR) less than 24 hours (14.7–23.8). The optimal time to commence out-of-bed activity remains unknown. While early animal studies showed that very-high-dose training within the first days poststroke increased brain lesion volume,[20] our recent animal meta-analysis[21] found that a shorter interval between stroke and exercise start reduced infarct volume (effect size −0.24, 95% CI −0.36 to −0.06, $p < 0.004$), without significantly influencing behavioral outcomes.[21] A further animal systematic review showed that early initiated (24–48 hours poststroke) moderate exercise reduced lesion volume and protected perilesional tissue against oxidative damage and inflammation.[22] Given that animal research to date suggests that activity within 24–48 hours of ischemic stroke onset may be helpful, an obvious translation gap exists.

Study strengths include that the dose-response analysis was prespecified[11] to help understand our complex intervention, and we had a strong focus on the quality of the nurse and physiotherapy data collected in the trial.[11] Our main limitation is that this exploratory analysis is not an RCT testing each of the intervention components separately (time, amount, frequency). Our results will need to be confirmed in further RCTs. Because we recorded physiotherapist-assisted out-of-bed therapy time only (not nursing), these data underestimate the actual minutes each day that a patient spent undertaking out-of-bed activity.

Table 3 Effect of intervention characteristics on favorable outcome (mRS 0–2) and unassisted walking

	Favorable outcome (mRS 0–2)		Walking unassisted 50 meters			
Efficacy	OR (95% CI)	p Value	Binary OR (95% CI)	p Value	Cox hazard ratio (95% CI)	p Value
Model 1						
Time to first mobilization (per extra hour)	0.99 (0.98–1.0)	0.036	1.0 (0.99–1.0)	0.40	0.99 (0.98–0.99)	<0.001
Frequency, median daily sessions[a] (per one extra session)	1.13 (1.09–1.18)	<0.001	1.66 (1.53–1.80)	<0.001	1.10 (1.09–1.13)	<0.001
Daily amount, median (per extra 5 minutes)	0.94 (0.91–0.97)	<0.001	0.85 (0.81–0.89)	<0.001	0.96 (0.94–0.97)	<0.001
Model 2						
Time to first mobilization (per extra hour)	0.99 (0.98–1.0)	0.025	1.0 (0.99–1.0)	0.48	0.99 (0.98–0.99)	<0.001
Frequency, median daily sessions[a] (per one extra session)	1.14 (1.10–1.18)	<0.001	1.63 (1.51–1.76)	<0.001	1.11 (1.10–1.13)	<0.001
Total amount[b] (per extra 5 minutes over intervention period)	0.99 (0.98–0.99)	<0.001	0.98 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; OR = odds ratio.
All analyses are adjusted for age and baseline NIH Stroke Scale score. Two models are shown. Model 1 includes examination of the effect of an extra 5 minutes of out-of-bed activity per day, while model 2 includes examination of the effect of an extra 5 minutes of out-of-bed activity over the intervention period to account for differences in length of hospital stay. Binary OR refers to walking 50 meters at 3 months vs not walking 50 meters at 3 months. That is, one extra session leads to fewer days required to walking 50 meters, while an extra 5 minutes daily session time is associated with more days to walking 50 meters.
[a] Frequency is derived from nursing and physiotherapist data.
[b] Amount (minutes) is derived from physiotherapist data only.

Table 4 Effect of intervention characteristics on death and nonfatal serious adverse events

	Safety							
	Deaths		Nonfatal SAEs		Fatal or nonfatal neurologic SAEs		Fatal or nonfatal immobility SAEs	
	Binary OR (95% CI)	*p* Value	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value	IRR (95% CI)	*p* Value
Model 1								
Time to first mobilization (per extra hour)	0.99 (0.98–1.00)	0.07	1.0 (0.99–1.00)	0.71	1.0 (0.99–1.00)	0.45	1.00 (0.99–1.00)	0.59
Frequency, median daily sessions[a] (per one extra session)	0.78 (0.70–0.88)	<0.01	0.99 (0.95–1.03)	0.55	0.89 (0.84–0.95)	0.001	0.94 (0.87–1.01)	0.11
Daily amount, median[b] (per extra 5 minutes)	0.96 (0.89–1.04)	0.30	0.96 (0.93–0.99)	0.01	1.03 (0.99–1.08)	0.17	0.94 (0.89–1.00)	0.06
Model 2								
Time to first mobilization (per extra hour)	0.99 (0.98–1.00)	0.07	0.99 (0.99–1.00)	0.81	1.00 (0.99–1.00)	0.35	1.00 (0.99–1.00)	0.59
Frequency, median daily sessions[a] (per one extra session)	0.79 (0.71–0.88)	<0.01	0.96 (0.93–0.99)	0.02	0.93 (0.88–0.98)	<0.01	0.91 (0.85–0.97)	<0.01
Total amount[b] (per extra 5 minutes over intervention period)	0.99 (0.98–1.00)	0.06	1.00 (1.00–1.00)	0.49	1.00 (0.99–1.00)	0.32	1.0 (0.99–1.00)	0.41

Abbreviations: CI = confidence interval; IRR = incident rate ratio; OR = odds ratio; SAE = serious adverse event.
All analyses are adjusted for age and baseline NIH Stroke Scale score. Two models are shown. Model 1 includes examination of the effect of an extra 5 minutes of out-of-bed activity per day, while model 2 includes examination of the effect of an extra 5 minutes of out-of-bed activity over the intervention period to account for differences in length of hospital stay. Immobility-related SAEs included deep vein thrombosis, pulmonary embolism, pressure sores, pneumonia, and urinary tract infection. Neurologic SAEs include stroke progression and recurrent stroke.
[a] Frequency is derived from nursing and physiotherapist data.
[b] Amount (minutes) is derived from physiotherapist data only.

One could argue that the intervention protocol influenced our findings because intervention dose was greater when participants had a less severe stroke. However, given that we found the same relationship between time to first mobilization, frequency, and amount of time in the usual care group alone as found for the whole group, this seems unlikely. That is, more frequent sessions (keeping mobilization time and median minutes of out-of-bed activity per day constant) improved the odds of a good outcome by 12% (OR 1.12, 95% CI 1.04–1.21, $p < 0.004$). Interestingly, less time to first mobilization was also associated with improved odds of a good outcome (OR 0.98, 95% CI 0.97–0.99, $p = 0.002$), while more minutes of out-of-bed activity was not (table e-1). Therefore, while the intervention protocol itself may have confounded some of this association, the results provide us with important clues on how the components of early and intensive rehabilitation affect outcome.

These results provide insights into the drivers of outcome and provide clinicians with a guide to early rehabilitation practices. There are 3 important messages from our results. The first is that physiotherapist- and nurse-facilitated mobility interventions delivered in the acute phase of care can change a patient's long-term outcomes, so it is critical that trialists carefully define and measure these interventions. Second, these results suggest that the frequency of intervention may be a more important driver of outcome. This has received little attention to date and requires further evaluation in future trials. The final message is that the currently accepted philosophy of "more practice is always better" needs to be reconsidered, particularly within the first days after stroke. The issue of timing, frequency, and amount of therapy is more complex that previously realized. This represents fertile ground for future research.

AUTHOR CONTRIBUTIONS

J. Bernhardt conceived and designed the study, wrote the first draft of the manuscript, and approved the final version. L. Churilov was the study statistician who prepared the analyses, reviewed the manuscript, and provided input. F. Ellery prepared the CART figures, reviewed the manuscript, and provided input. J. Collier reviewed the manuscript and provided input. J. Chamberlain reviewed the manuscript and provided input. P. Langhorne reviewed the manuscript and provided input. R.I. Lindley reviewed the manuscript and provided input. M. Moodie reviewed the manuscript and provided input. H. Dewey reviewed the manuscript and provided input. A.G. Thrift reviewed the manuscript and provided input. G. Donnan reviewed the manuscript and provided input.

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