A Very Early Rehabilitation Trial for Stroke (AVERT)
Phase II Safety and Feasibility

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Background and Purpose—Very early rehabilitation, with an emphasis on mobilization, may contribute to improved outcomes after stroke. We hypothesized that a very early rehabilitation protocol would be safe and feasible.

Methods—We performed a randomized, controlled trial with blinded outcome assessment. Patients at <24 hours after stroke were recruited from 2 Melbourne metropolitan stroke units. Patients were randomly assigned to receive standard care (SC) or SC plus very early mobilization (VEM) until discharge or 14 days (whichever was sooner). The primary safety outcome was the number of deaths at 3 months. The primary feasibility outcome was a higher “dose” of mobilization achieved in VEM. Secondary safety outcomes included adverse events (including falls and early neurologic deterioration), compliance with physiologic monitoring criteria, and patient fatigue after interventions. Secondary feasibility outcomes included “contamination” of standard care.

Results—Overall, 18% of patients screened were suitable for recruitment. Seventy-one patients were recruited and randomized, with 2 dropouts by 12 months. The majority experienced ischemic strokes (87%). The group mean ± SD age was 74.7 ± 12.5 years, and 58% (n = 41) had a National Institutes of Health Stroke Scale score ≥ 7. There was no significant difference in the number of deaths between groups (SC, 3 of 33; VEM, 8 of 38; P = 0.20). Almost all deaths occurred in patients with severe stroke. Secondary safety outcomes were similar between groups. The intervention protocol was successfully delivered, achieving VEM dose targets (double SC, P = 0.003) and faster time to first mobilization (P < 0.001).

Conclusions—VEM of patients within 24 hours of acute stroke appears safe and feasible. Intervention efficacy and cost-effectiveness are currently being tested in a large randomized, controlled trial. (Stroke. 2008;39:390-396.)

Key Words: cerebrovascular accident ■ rehabilitation ■ early ambulation ■ phase II clinical trial ■ randomized controlled trial

There is considerable evidence that management of patients after stroke in a stroke unit reduces mortality and improves functional outcome.1,2 However, there is uncertainty about which components of stroke unit care contribute to this benefit. In a retrospective analysis of patients who received stroke unit rather than general medical ward care, the greatest contributors to better outcome appeared to be very early mobilization (VEM; getting patients out of bed within 24 hours of stroke onset) and better blood pressure control.3 Previous investigations of VEM versus delayed mobilization have provided inconclusive results; however, power was limited.4,5 Despite this inconclusive evidence, VEM has been promoted within a number of published stroke guidelines,6,7 although the practice remains controversial.8,9 In our own observational study conducted in 5 acute stroke units in Melbourne during 2002, we found that acute stroke patients were mobilized little, spending >50% of the day resting in bed.10,11

Given that VEM represents a simple intervention that may be suitable for a large proportion of the stroke population, we determined that a randomized, controlled trial comparing VEM with standard care (SC) was indicated. The cost-effectiveness of the intervention should also be determined. As a first step, data concerning the feasibility and safety of this approach were required. We hypothesized that a very early rehabilitation protocol, with a focus on mobilization, was safe and feasible to administer across multiple sites.
Subjects and Methods

Study Setting
The study setting was acute stroke units at 2 large teaching hospitals in metropolitan Melbourne, Australia. These acute stroke units had multidisciplinary teams with an interest in stroke and regular team meetings, as well as access to 24-hour computed tomography and intensive care units.

Study Design
We used a prospective, open, randomized, controlled-trial, blinded-outcome assessment design.12

Inclusion Criteria
Patients >18 years with a first or recurrent stroke, as defined by the World Health Organization,13 admitted within 24 hours of symptom onset were sought. To be eligible, stroke patients were required to react to verbal commands (but did not need to be fully alert) and to have a systolic blood pressure between 120 and 220 mm Hg, an oxygen saturation of >92% (with or without supplementation), a heart rate between 40 and 100 beats per minute, and a temperature <38.5°C.

Exclusion Criteria
Patients with a premorbid (retrospective) modified Rankin Scale (mRS) score14 >3, deterioration within the first hour of admission to the stroke unit or direct admission to intensive care, a concurrent progressive neurologic disorder, acute coronary syndrome, severe heart failure, confirmed or suspected lower-limb fracture preventing mobilization, and those requiring palliative care were excluded. Ethics committees of both institutions approved the study, and informed consent was obtained from all participants or their representatives. Approval allowed concealment of group allocation from the patients.

Randomization
We used computer-generated, blocked randomization procedures with stratification by stroke severity and clinical site. Opaque envelopes concealed the group allocation. The National Institutes of Health Stroke Scale (NIHSS) administered by trained assessors was used to determine stroke severity with the following cutpoints: mild (NIHSS <8), moderate (NIHSS, 8 to 16), and severe (NIHSS >16).15 We aimed to recruit equal numbers of patients with mild, moderate, and severe stroke.

Intervention
Patients randomized to the VEM group commenced mobilization as soon as practical after recruitment, with the goal of first mobilization within 24 hours of stroke symptom onset. VEM continued daily for the first 14 days after stroke or until discharge (whichever was sooner) and was delivered by a nurse/physiotherapist team as set out in a detailed intervention protocol. The protocol included physiologic monitoring of blood pressure, heart rate, oxygen saturation, and temperature before each mobilization within the first 3 days of stroke. The emphasis of VEM was to assist the patient to be upright and out of bed (sitting or standing as able) at least twice per day; in addition to their usual care, 6

Blinding
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. The importance of maintaining blinding was emphasized to trial staff, and interventions provided by them were not recorded in the medical record. All outcomes were assessed by a blinded assessor located off-site. When the patient was still in hospital at the 7- and 14-day assessments, trial staff were informed so that the blinded assessor would not inadvertently view an intervention.

Baseline Data
Patient characteristics collected at baseline included demographic (age, sex, and country of birth) and stroke (type, side, and site of stroke; first or recurrent stroke; stroke severity as per NIHSS15,18) factors; vascular risk factors; stroke classification according to the Oxfordshire Community Stroke Project classification19, and neglect as assessed by the star cancellation test. Premorbid disability (as per mRS) and living arrangements before stroke were documented. Assessors were trained and accredited in the use of the mRS.20 Cerebral imaging findings were recorded.

Outcome Assessment
Patients were visited and assessed at 7 and 14 days and at 3, 6, and 12 months. Different primary and secondary outcomes were assessed at selected time points. In addition to the outcomes listed next, disability (as per mRS) was also assessed at 3, 6, and 12 months. Good outcome was predefined as an mRS score of 0 to 2 and poor outcome, as an mRS score of 3 to 6.

Primary Outcome Measures
The primary safety outcome was death at 3 months. The cause of death was determined by blinded review of the clinical details by the investigators and those obtained from the death certificate. The primary feasibility outcome was achievement of a significant difference in the total dose of mobilization between groups. Both the minutes of therapy and patient position during therapy were recorded by ward therapists and trial therapists with personal digital assistants (Palm Zire 21 Handheld). This allowed calculation of the total dose of mobilization for each group.

Secondary Outcome Measures
Secondary safety end points included the following: (1) The number of serious adverse events at 3 months. These were defined as any event that was life threatening, was incapacitating, or prolonged hospital admission or patient acuity. Falls were classified as serious if they resulted in fracture, head injury, or other criteria for a serious adverse event. The number of falls during stroke unit stay (maximum, 14 days) and at 3 months is reported. (2) Deterioration within the first 7 days according to the European Progressing Stroke Study definition.21,22 A point worsening ≥2 on the Scandinavian Stroke Scale in either consciousness level or arm, leg, or eye movement scores and/or a ≥3-point worsening on the Scandinavian Stroke Scale in speech score. (3) Patients’ perceived exertion after treatment. This was measured with the Borg Perceived Exertion scale.23 We defined excessive fatigue as any score >13 (“somewhat hard”). (4) The number of occasions on which patients randomized to VEM were prevented from continuing with the per-protocol treatment because of 3 consecutive drops in systolic blood pressure ≥30 mm Hg.

Secondary feasibility outcomes were time from stroke onset to first mobilization and observed increases in the delivery of mobilization to a random sample of stroke unit patients during the conduct of the trial (“contamination”).

Contamination
To determine whether the provision of VEM to trial patients on the stroke units led to delivery of the intervention to other patients.
not involved in the trial (i.e., contamination), we undertook intermittent monitoring of physical activity patterns of these other patients. Research staff external to the clinical trial recorded activity data with the behavioral mapping protocol used previously. Data from that earlier study served as a baseline, allowing us to monitor change over time. A reduction in bed rest of \( \frac{5}{100} \) from baseline and/or a \( \frac{5}{100} \) increase in time spent standing and walking during the active day (8 AM to 5 PM) were set as clinical indicators that contamination might have occurred.

To assess whether protocols to blind the assessor to group were effective, at the 7-day assessment the blinded assessor was asked to select (forced choice) to which group they thought the patient had been allocated. This procedure was introduced in the third month of the study.

**Data Management**

Case report forms were created in Teleform. Forms were scanned and visually checked, with electronic data transfer into Microsoft Access 1997. Pendragon Forms 4.0 on a personal digital assistant were used to record all therapy data.

**Statistical Analyses**

Safety, feasibility, and disability analyses were conducted on an intention-to-treat basis. A standard level of significance (\( P<0.05 \)) was used. Fisher’s exact test was used for analysis of death at 3 months. Disability outcomes were analyzed with both unadjusted (Fisher’s exact) and adjusted (age, premorbid mRS score, and NIHSS score on admission) outcomes (multivariable logistic regression).

Deterioration and perceived exertion were evaluated with Fisher’s exact test. The number of falls and other serious adverse events were compared by Poisson regression. When data were in interval form but not normally distributed (e.g., dose and time to first mobilization, length of stay), a nonparametric equality of medians test was used.

Contamination was examined by comparing stroke unit data obtained during this Phase II trial with pretrial data. Logistic-regression analysis was used to evaluate change over time in the proportion of the day spent in either standing and walking activities or resting in bed, while controlling for differences in patient characteristics between time periods. Patient characteristics included sex, age, first stroke, days after stroke, stroke severity (as per NIHSS), and mobility level. To determine whether the blinded assessor guess of treatment group at 7 days after stroke was better than chance, we performed a 2-sample test of proportions. All analyses were conducted with STATA version 9.1 (STATA Corp).

**Results**

During open recruitment of patients with all stroke severities, 315 hospital-admitted stroke patients were screened, and 18% of the population was recruited (n=56). No patient declined to participate in the trial. Fifty-seven percent of patients (n=180) failed to meet the inclusion criteria, most often because they had reached the hospital 24 hours after stroke symptom onset (31% of all patients, n=98). We missed screening 19% of patients (n=60) because they presented after hours or on the weekend, and the final 6% (n=19) were recruited to other trials. Patients who experienced mild stroke (NIHSS score <8) were recruited rapidly. To limit imbalance with respect to stroke severity, recruitment of these patients ceased in October 2004, and thereafter only patients with moderate and severe stroke were recruited.
A total of 71 patients were recruited as follows: 60 from the Austin Hospital between March 2004 and February 2006 and 11 from St. Vincent’s Hospital between May 2005 and February 2006. Most patients were born in Australia (68%, n=48). The other 32% (n=23) were born elsewhere (Italy 15%, n=11; Greece 4%, n=3; and other 13%, n=9). Just over half (53.5%, n=38) provided consent for themselves. The remainder required a person responsible to consent on their behalf. Mean±SD group age was 74.7±12.5 years with a mean NIHSS score at entry of 10±6.9, and ischemic stroke was the most common type (87%, n=62). Enrollment and retention throughout the trial are shown in Figure 1. Only 2 patients were lost to follow-up at 12 months.

Baseline characteristics were similar between the groups (Table 1) with no significant differences found. Notably, 58% (n=41) of the sample had moderate or severe stroke. Hospital length of stay was also similar for both groups (VEM median [range]=6 [1–51] days; SC median [range]=7 [1–26] days; P=0.31).

### Primary Outcomes

#### Safety

Overall, 11 patients (15.5%) were dead at 3 months after stroke. More patients in the VEM group died (VEM, 8 of 38 vs SC, 3 of 33; absolute risk difference=12.0%; 95% CI, −4.3% to 28.2%, P=0.20). Those who died were more severely affected (baseline NIHSS score: median 22, range 9 to 24) than those who survived (baseline NIHSS score: median 8, range 1 to 24). Six of the 11 deaths occurred during the acute poststroke period (≤14 days) and were due to stroke. The remaining 5 deaths from day 15 to 3 months were also due to stroke. Post hoc analysis was performed after adjusting for the baseline imbalance in stroke severity and premorbid mRS scores (data not shown). There was no significant difference in deaths between the 2 groups, and the CIs were wide.

#### Feasibility

The total dose (median, IQR) of mobilization achieved in the VEM group was double that of SC (VEM 167 minutes, 62 to 305; SC 69 minutes, 31 to 115; P=0.003; Figure 2). The median time to first mobilization 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 SC group (P<0.001).

### Secondary Outcomes

#### Safety

The total number of serious adverse events at 3 months (not including death) was similar between groups (VEM=15, SC=14, P=0.846). Serious adverse events included stroke progression (n=7), pneumonia (n=7), recurrent stroke (n=1), myocardial infarction (n=2), atrial fibrillation (n=1), and other (n=11). At 3 months, there were significantly fewer nonserious adverse events experienced by patients in the VEM group (VEM=61, SC=76, P=0.04).

Falls were considered a separate subset of adverse events. There was no difference in fall rate between groups during the intervention period: VEM=19.7/1000 bed-days

| Table 1. Baseline Characteristics of Recruited Patients |
|---|---|---|---|
| | SC, n=33 | VEM, n=38 | All Patients, n=71 |
| Age, mean (SD) | 74.9 (9.8) | 74.6 (14.6) | 74.7 (12.5) |
| Female | 17 (53) | 16 (42) | 33 (46) |
| Stroke risk factors | | | |
| Hypertension | 25 (76) | 25 (66) | 50 (70) |
| Ischemic heart disease | 13 (39) | 7 (18) | 20 (28) |
| Angina | 9 (27) | 5 (13) | 14 (20) |
| Hypercholesteremia | 11 (33) | 8 (21) | 19 (27) |
| Diabetes | 4 (12) | 11 (29) | 15 (21) |
| Smoking | | | |
| Never smoked | 15 (45) | 15 (47) | 30 (46) |
| Smoker* | 6 (18) | 7 (22) | 13 (20) |
| Former smoker* | 12 (36) | 10 (31) | 22 (34) |
| Unknown | 0 (0) | 6 (16) | 6 (8) |
| Factors limiting mobilization | | | |
| Respiratory† | 5 (15) | 4 (11) | 9 (13) |
| Lower limb‡ | 7 (21) | 11 (29) | 18 (25) |
| Premorbid history | | | |
| Premorbid mRS score | | | |
| 0 | 20 (61) | 18 (47) | 38 (54) |
| 1 | 8 (24) | 6 (16) | 14 (20) |
| 2 | 2 (6) | 8 (21) | 10 (14) |
| 3 | 3 (9) | 6 (16) | 9 (13) |
| Living arrangement at time of admission | | | |
| Home alone | 7 (21) | 4 (11) | 11 (15) |
| Home with someone | 25 (76) | 30 (79) | 55 (78) |
| Hostel | 1 (3) | 4 (11) | 5 (7) |
| Stroke history | | | |
| First stroke | 26 (79) | 27 (71) | 53 (75) |
| Side of lesion (left) | 14 (42) | 22 (58) | 36 (51) |
| NIHSS score | | | |
| Mild (1–7) | 15 (46) | 15 (39) | 30 (42) |
| Moderate (8–16) | 11 (33) | 13 (34) | 24 (34) |
| Severe (>16) | 7 (21) | 10 (26) | 17 (24) |
| All cases: mean (SD) | 9 (6.5) | 11 (7.2) | 10 (6.9) |

*Smoker was defined as current smoker or one who had quit smoking in the previous 2 years. Former smoker was defined as one who had quit >2 years ago.
†Respiratory limiting factors were emphysema/chronic obstructive airway disease.
‡Lower-limb limiting factors were lower-limb arthritis or lower-limb joint replacement. No subjects had a lower-limb amputation.
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Deterioration between groups from day 0 to day 7 (95% CI, −2.1 to 41.4); SC = 22.8/1000 bed-days (95% CI, 0.4 to 45.3, \( P < 0.81 \)). Two serious falls were reported for 1 patient in the VEM group during the first 3 months after stroke. However, these occurred after the acute intervention period. There was no significant difference in the total number of falls recorded up to 3 months after stroke (VEM = 27, SC = 28, \( P = 0.51 \)). There was no difference in deterioration between groups from day 0 to day 7 (VEM = 8, SC = 9, \( P = 0.78 \)).

Twenty patients were unable to complete at least 1 assessment of perceived exertion after intervention because of comprehension, consciousness, or language difficulties. Fifty-one patients completed the Borg assessment (VEM \( n = 30, \ SC = 21 \)). Similar proportions of patients in the VEM and SC groups reported excessive fatigue (Borg score > 13; VEM = 28.6%, SC = 23.3%, \( P = 0.75 \)). No patient had 3 consecutive drops in blood pressure > 30 mm Hg during the first 3 attempted mobilizations. Interestingly, no patient or caregiver requested information about their treatment group.

**Disability**

More patients in the VEM group had a good outcome at 3 months (VEM = 39.5%, SC = 30.3%); however, this difference was not statistically significant (Table 2). The absolute risk difference was 9.2% (95% CI, −12.9% to 31.2%, \( P = 0.46 \)). At 6 and 12 months after stroke, there was no significant difference in having a good outcome between groups (odds ratio = 1.36; 95% CI, 0.51 to 3.65, \( P = 0.54 \) and odds ratio = 1.99; 95% CI, 0.70 to 5.63, respectively; \( P = 0.20 \)) in univariable analyses. After adjusting for baseline variables (age, premorbid mRS score, and NIHSS score on admission), the odds of a good outcome appeared greater in the VEM group than the SC group at 3, 6, and 12 months (Table 2); however, only the differences at 12 months were significant.

**Feasibility**

The assessor attempted to guess group allocation at 7 days after stroke for 56 patients. A correct guess was made in 34 cases. By chance alone, the assessor was expected to correctly guess group allocation in 28 cases. The actual guess was no better than chance (\( P = 0.25 \)). Fifty-one patients participated in the separate study to assess contamination among nontrial patients. There was no evidence for an increase in the proportion of the day spent in standing and walking activities (95% CI, −0.06 to 0.02, \( P = 0.32 \)) between the 2 time intervals. There was also no evidence of a decrease in time spent resting in bed (95% CI, −0.02 to 0.02, \( P = 0.93 \)).

**Discussion**

In this study, we found that a randomized trial of very early treatment for acute stroke patients was both safe and feasible. The inclusion criteria for entry into the study were broader than those used in many other acute stroke trials, with no upper age limit and unrestricted NIHSS score on admission. Due consideration was given, however, to applying reasonable physiologic limits for participation. The absence of an upper age limit to trial participation was intentional, given that it was reasonable to expect that stroke patients, regardless of age, would be able to participate in simple walking and standing activity with the assistance of trained healthcare professionals. Furthermore, we wished to test the intervention in a broad range of stroke patients receiving routine clinical care. Patient demographics, with the exception of an intentionally high proportion of patients with moderate and severe stroke, were representative of acute stroke unit populations.27,28

![Box-and-whisker plots of mobilization dose and time to first mobilization. The middle bar represents the median value, with 25th and 75th percentiles represented by the upper and lower boundaries, respectively, of the box. Values outside these limits are represented by bars, with extreme cases represented by circles and stars. Mobilization commenced earlier, with a higher dose in the VEM group (\( P < 0.05 \)).](image-url)

**Table 2. Good Outcome (mRS score 0–2) at 3, 6, and 12 Months After Stroke**

<table>
<thead>
<tr>
<th>Good Outcome (mRS 0–2)</th>
<th>SC, n/N (%)</th>
<th>VEM, n/N (%)</th>
<th>Univariable ( P )</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>10/33 (30.3)</td>
<td>15/38 (39.5)</td>
<td>0.46</td>
<td>4.10 (0.99–16.88)</td>
<td>0.05</td>
</tr>
<tr>
<td>6 months</td>
<td>11/32 (34.4)</td>
<td>15/36 (41.7)</td>
<td>0.62</td>
<td>4.17 (0.87–20.07)</td>
<td>0.08</td>
</tr>
<tr>
<td>12 months</td>
<td>8/33 (24.2)</td>
<td>14/36 (38.9)</td>
<td>0.21</td>
<td>8.15 (1.61–41.21)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

*Adjusted for age, baseline NIHSS score, and premorbid mRS score.
We found no significant difference in the primary safety outcome measure of death between VEM and SC groups. An overall case fatality of 15.5% at 3 months compares favorably with the 28-day case fatality of 20% found in a population-based stroke incidence study undertaken in a similar study area.27 Thus, deaths in either group did not occur more often than would be expected in a representative sample of patients and were considerably less than expected in the SC group. This is likely to be attributable to chance alone. However, the study was small. The true risks and benefits of this early intervention will be determined only through the conduct of a larger Phase III study, and ongoing monitoring of deaths and serious adverse events by an independent committee will be necessary. Importantly, there was no difference in the proportion of patients with early neurologic deterioration. Also, excessive fatigue and physiologic intolerance were not barriers to the delivery of VEM.

We succeeded in recruiting patients and commencing intervention for those randomized to the intervention arm within 24 hours of stroke. Treatments were delivered as set out in the protocol in the majority of cases. Furthermore, during recruitment of patients of all stroke severities, we recruited 18% of patients to this study. This rate is high in comparison with many other acute stroke trials,28 likely due to our broader inclusion criteria. The major exclusion was failure to arrive at the hospital within the first 24 hours of symptom onset (31%).

Although disability outcomes were not the primary focus of this study, we found a nonsignificant 9.2% risk difference at 3 months after stroke. Earlier sample size estimates for the planned Phase III study to determine efficacy and cost-effectiveness were based on a 7.1% risk difference between groups,30 resulting in a total required sample of 2104 patients. The present study has confirmed that the initial sample size estimates were appropriate.

We found no evidence of changes in usual practice in response to the presence of the trial (contamination). This is an important finding, as patients receiving intervention care and SC managed in the same ward are susceptible to contamination bias.30

Summary
The AVERT protocol in which mobilization commences within 24 hours of symptom onset appears both safe and feasible. Given that early mobilization may be 1 of the simplest yet most important components of effective stroke unit care, this intervention requires testing in a large randomized, controlled trial. The AVERT Phase III efficacy and cost-effectiveness study31 commenced in July 2006.

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Disclosures
None.

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