Very Early Mobilization After Stroke Fast-Tracks Return to Walking

Further Results From the Phase II AVERT Randomized Controlled Trial

Toby B. Cumming, PhD; Amanda G. Thrift, PhD; Janice M. Collier, PhD; Leonid Churilov, PhD; Helen M. Dewey, PhD; Geoffrey A. Donnan, MD; Julie Bernhardt, PhD

Background and Purpose—Regaining functional independence is an important goal for people who have experienced stroke. We hypothesized that introducing earlier and more intensive out-of-bed activity after stroke would reduce time to unassisted walking and improve independence in activities of daily living.

Methods—A Very Early Rehabilitation Trial (AVERT) was a phase II randomized controlled trial. Patients with confirmed stroke (infarct or hemorrhage) admitted <24 hours after stroke and who met physiological safety criteria were eligible. Patients randomized to the very early and intensive mobilization group were mobilized within 24 hours of stroke and at regular intervals thereafter. Control patients received standard stroke unit care. The primary outcome for this analysis was the number of days required to return to walking 50 m unassisted. Secondary outcomes were the Barthel Index and Rivermead Motor Assessment at 3 and 12 months after stroke.

Results—Seventy-one stroke patients with a mean age of 74.7 years were recruited from 2 hospitals. Adjusted Cox regression indicated that very early and intensive mobilization group patients returned to walking significantly faster than did standard stroke unit care controls ($P=0.032$; median 3.5 vs 7.0 days). Multivariable regression revealed that exposure to very early and intensive mobilization was independently associated with good functional outcome on the Barthel Index at 3 months ($P=0.008$) and on the Rivermead Motor Assessment at 3 ($P=0.050$) and 12 ($P=0.024$) months.

Conclusions—Earlier and more intensive mobilization after stroke may fast-track return to unassisted walking and improve functional recovery.

Clinical Trial Registration—This trial was not registered because enrollment began before July 2005.

(Stroke. 2011;42:153-158.)

Key Words: acute care ■ cerebrovascular disease ■ functional recovery ■ randomized controlled trials ■ rehabilitation
general medical ward. Walking recovery was not specifically measured in this study, but a post hoc analysis indicated that a shorter time to start of mobilization after stroke onset was the most important factor associated with discharge to home. Given the general lack of physical activity in the first weeks after stroke, we believed that there was an opportunity to introduce earlier and more frequent mobilization. The safety and feasibility of this intervention were the primary outcomes tested as part of a phase II clinical trial comparing a very early and intense mobilization protocol (VEM) with standard stroke unit care (SC).

In the current article, we report the outcomes associated with recovery of walking and independence in ADLs. We hypothesized that patients in the VEM group would walk unassisted sooner than SC controls. We also hypothesized that VEM patients would achieve better functional independence (as measured by the Barthel Index and Rivermead Motor Assessment) than SC controls at 3 and 12 months after stroke.

**Methods**

**Design**

A Very Early Rehabilitation Trial (AVERT) phase II was a prospective randomized controlled trial with concealed allocation, blinded assessment of outcomes, and intention-to-treat analysis. The setting was the acute stroke units of 2 large hospitals in Melbourne, Australia. Ethics approval was obtained. The methods have been reported in detail elsewhere and are summarized in the subsequent paragraphs.

**Population**

Patients were included if they (1) were ≥18 years; (2) satisfied physiological limits (systolic blood pressure 120 to 220 mm Hg, heart rate 40 to 100 bpm, oxygen saturation >92%, and temperature <38.5°C); and (3) could be randomized within 24 hours of symptom onset of a first or recurrent stroke. Patients were excluded if they had a premorbid modified Rankin Scale (mRS) score >3 (indicating disability), deterioration within the first hour of admission to the stroke unit or direct admission to intensive care, concurrent progressive neurological disorder, acute coronary syndrome, severe heart failure, lower-limb fracture that prevented mobilization, or required palliative care.

**Procedure**

When discussing informed consent, patients were told that they would be given 1 of 2 different types of rehabilitation. Computer-generated, blocked randomization procedures and concealment with opaque envelopes were used to allocate patients to either the VEM or SC group. Randomization was stratified by hospital site and stroke type and dose of therapy for both groups were recorded on personal digital assistants. Occupational health and safety procedures for manual handling of patients were maintained. Blood pressure, heart rate, oxygen saturation, and temperature were monitored before the first 3 mobilizations of VEM patients. “Contamination” of standard care was monitored throughout the study.

**Baseline Assessment**

Baseline assessment included age, sex, stroke type according to the Oxfordshire stroke classification, stroke severity on the NIHSS, diabetes status as well as other stroke risk factors, pre-stroke living arrangements, and pre-stroke functional level on the mRS. The mobility scale for acute stroke was used to establish baseline restrictions in a patient’s ability to move in bed, sit up, and walk 10 m, and information from this scale was used to guide the VEM intervention level.

**Outcome Measures**

Assessments by the blinded assessor took place at 7 and 14 days and 3, 6, and 12 months after stroke. For this data analysis, the main outcome of interest was time to walking 50 m. This was defined as the number of days from stroke onset until the patient could first walk 50 m without human assistance, a distance used in the Functional Independence Measure walking item and commonly marked out within hospital departments. To remove the subjectivity associated with both the need for supervision (Functional Independence Measure score 5) and walking aid (Functional Independence Measure score 6), we defined walking as “walking unassisted by human help (gait aid allowed) for a continuous distance of 50 meters.” Physiotherapists were responsible for completion of the 50-m walk.

The other outcome measures were the Barthel Index and Rivermead Motor Assessment, both assessed at 3 and 12 months after stroke. The Barthel Index, a valid and reliable measure of ADLs in stroke research, was used to assess independence in 10 everyday activities. The total score sums to 20, and higher scores reflect better performance. As per common practice with the Barthel Index, patients were classified as either independent (score=20) or dependent (score=0 to 19) in ADLs. The Rivermead Motor Assessment gross function scale of 13 items was used to examine motor activity and has established reliability in stroke. It includes easy and difficult items, with the first item testing unsupported sitting, and other items testing ability to transfer, walk indoors, walk outdoors, run, and hop on the spot. The best performance of 3 trials on each item was scored, with a score of 0 indicating that the patient was unable to perform any of the activities independently and a score of 13 indicating independence with all activities. Patients were classified as either impaired (score=0 to 9) or not impaired (score=10 to 13) in motor activity, a cutoff chosen to align with the clinically meaningful ability to walk outside the home (community ambulation).

**Statistical Analysis**

A sample of 70 patients was deemed sufficient to allow examination of the primary safety outcome of the study (death) at 3 months after stroke. Although the study was not powered to detect differences in physical outcomes reported in this article, an important part of feasibility testing includes evaluation of performance and utility of the outcome measures used.

Because one third of stroke patients die in the first 12 months, analyses must deal with missing data due to deaths. Furthermore, when inclusion criteria are broad, as in this trial, stroke symptoms can vary markedly, with the result that some patients will fail to achieve any score on a given test, particularly those related to higher levels of activity. Excluding patients who died or who failed to achieve a score on a test would bias results, and imputing data values for these subjects requires guesswork. In this study, all patients who died were assigned a score of 0 on the Barthel and Rivermead scales for all subsequent time points. A score of 0 was deemed likely to reflect their status had they still been alive, given that people who die in the first year after stroke are more likely to have had a severe stroke (and would be expected to have a very low score on these measures). Patients alive at the time of assessment with missing data...
were not included in analyses. Multivariable analyses were used to account for demographic and stroke-related factors known to influence walking and functional independence (age, stroke severity, and diabetes) and other factors that may also impact these outcomes (sex and premorbid disability).

**Days to Walking**
The number of days between stroke onset and a 50-m unassisted walk was recorded. A Cox regression was performed with adjustment for important prognostic variables (age, sex, NIHSS, premorbid mRS and diabetes).

**Barthel Index**
Mann-Whitney U tests were used to assess between-group differences in Barthel score. Barthel data were then used to classify patients as either independent or dependent in ADLs, and Fisher’s exact tests were used to detect group differences. Multivariable logistic-regression analyses, with the Barthel Index as the binary outcome measure, were then performed to determine the effect of group (VEM or SC), age, sex, NIHSS, premorbid mRS and diabetes on independence in ADLs.

**Rivermead Motor Assessment**
Between-group differences in Rivermead scores were analyzed by Mann-Whitney U tests. Rivermead data were then used to classify patients as either impaired or not impaired in motor activity, and Fisher’s exact tests were used to detect group differences. Multivariable logistic-regression analyses were then performed on the binary Rivermead data in the same way as described for the Barthel Index.

**Results**
Seventy-one patients were recruited from 2004 to 2006: 60 from the Austin Hospital and 11 from St. Vincent’s Hospital (Figure 1). Baseline characteristics between groups were similar (Table 1). Notably, 58% of the sample had moderate or severe stroke. Median time to mobilization was shorter in VEM (18 hours) than in SC (31 hours), and the median total dose of mobilization was greater for VEM (167 minutes) than for SC (69 minutes). By 3 months, 11 patients (15%) had died, and at 12 months, 17 patients (24%) had died. The proportion of deaths between groups was not different and was low compared with population-based studies. Three surviving patients had missing data, but inspection of their characteristics showed that any systematic bias was unlikely. They were not all from one group (2 VEM, 1 SC), they had a range of ages (58, 82, and 86 years), and they did not have severe stroke (NIHSS of 1, 5 and 7).

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Recruited Patients</th>
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<tbody>
<tr>
<td><strong>SC</strong></td>
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<tr>
<td>No. (%)</td>
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<tr>
<td>Patient details</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Stroke details</td>
</tr>
<tr>
<td>Left-sided lesion</td>
</tr>
<tr>
<td>NIHSS score</td>
</tr>
<tr>
<td>Mild (1–7)</td>
</tr>
<tr>
<td>Moderate (8–16)</td>
</tr>
<tr>
<td>Severe (&gt;16)</td>
</tr>
<tr>
<td>Oxfordshire Stroke Classification</td>
</tr>
<tr>
<td>TACI</td>
</tr>
<tr>
<td>PACI</td>
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<tr>
<td>POCI</td>
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<tr>
<td>LACI</td>
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<tr>
<td>ICH</td>
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<tr>
<td>Prior history of stroke</td>
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<td>Stroke risk factors</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Ischemic heart disease</td>
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<td>Angina</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Never smoked</td>
</tr>
<tr>
<td>Smoker†</td>
</tr>
<tr>
<td>Ex-smoker†</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Factors limiting mobilization</td>
</tr>
<tr>
<td>Respiratory‡</td>
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<tr>
<td>Lower limb§</td>
</tr>
<tr>
<td>Premorbid history</td>
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<tr>
<td>Premorbid mRS</td>
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<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

*No. (percent) unless otherwise indicated.
†Smoker= current smoker or who quit within the last 2 years. Ex-smoker= quit >2 years ago.
‡Respiratory limiting factors included emphysema and chronic obstructive airway disease.
§Lower-limb limiting factors included lower-limb arthritis and lower-limb joint replacement.
Days to Walking
On admission, 86% of patients could not walk or required hands-on assistance to walk short distances (mobility scale for acute stroke gait score 1 to 4; VEM n=34, SC n=27). Only 14% of patients were rated as able to walk with supervision (VEM n=4, SC n=6). Median days taken to return to walking 50 m was 3.5 (interquartile range [IQR] = 1.5 to 14.0) in the VEM group and 7.0 (IQR = 2.0 to 20.0) in the SC group. At 2 weeks after stroke (the end of the intervention period) among surviving patients, 67% (22 of 33) of the VEM group had returned to unassisted walking compared with 50% (16 of 32) of the SC group. Results of the Cox regression analysis, with adjustment for potentially confounding variables, demonstrated a significant impact of the intervention on time to walking (P = 0.032; Table 2). The log-minus-log function indicated that the assumption of proportionality was met. Patients in the VEM group returned to independent walking sooner than did SC patients, as shown in the adjusted survival curves (Figure 2). Earlier return to walking after stroke was also independently associated with less severe stroke (NIHSS), younger age, and absence of diabetes (Table 2).

Barthel Index
Proxy respondents provided answers for 21% of 3-month survivors and 17% of 12-month survivors (primarily due to the patient having communication difficulties). The distribution of Barthel scores was bimodal, with most patients clustered at either the low or high end of the scale. Scores on the Barthel Index at 3 months were higher for the VEM group (median = 18.5, IQR = 2.0 to 20.0) than the SC group (median = 16.5, IQR = 9.0 to 20.0), but this difference was not significant (P = 0.713). In VEM, 47% (17 of 36) of patients had a good outcome on the Barthel Index at 3 months compared with 28% (9/32) of SC patients (P = 0.136). Scores on the Barthel Index at 12 months were not significantly different between groups, with 39% of patients having a good outcome in both VEM (median = 18.0, IQR = 0.0 to 20.0) and SC (median = 18.0, IQR = 7.0 to 20.0) groups. In multiple regression analysis, having a good outcome on the Barthel Index at 3 months was independently associated with exposure to VEM, less severe stroke on admission (NIHSS), and younger age. Having a good Barthel outcome at 12 months was independently associated with less severe stroke, younger age, male sex, and absence of diabetes, but the effect of exposure to VEM was no longer apparent (Table 3). Results were similar when the analyses were restricted to survivors only (data not shown).

Rivermead Motor Assessment
Scores on the Rivermead assessment at 3 months were similar in VEM (median = 10.0, IQR = 5.0 to 11.0) and SC (median = 10.0, IQR = 3.0 to 11.0) groups (P = 0.883). In VEM, 62% (23 of 37) of patients had a good Rivermead outcome at 3 months compared with 56% (18 of 32) of SC patients (P = 0.633). Scores on the Rivermead at 12 months were not significantly different between groups, with 53% of VEM patients having a good outcome (median = 10.0, IQR = 0.0 to 11.0) compared with 45% of SC patients (median = 9.0, IQR = 1.0 to 11.0). In multiple regression, having a good Rivermead outcome was independently associated with exposure to VEM, less severe stroke (NIHSS), and younger age, at both 3 and 12 months (Table 4). Results were similar when the analyses were restricted to survivors only, although age was no longer associated with good outcome (data not shown).

Discussion
The most important finding was that stroke patients who received VEM in addition to standard stroke unit care were

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### Table 2. Cox Regression for No. of Days to Walking 50 m Unassisted (N=71)

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEM</td>
<td>0.523</td>
<td>0.289</td>
<td>0.945</td>
<td>0.032</td>
</tr>
<tr>
<td>Age</td>
<td>0.967</td>
<td>0.944</td>
<td>0.990</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td>0.679</td>
<td>0.374</td>
<td>1.233</td>
<td>0.204</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.864</td>
<td>0.815</td>
<td>0.916</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>0.867</td>
<td>0.645</td>
<td>1.165</td>
<td>0.344</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.147</td>
<td>1.020</td>
<td>4.520</td>
<td>0.044</td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Binary Logistic Regressions, With Independence in ADLs (Barthel Index=20 vs Barthel Index=0–19) at 3 and 12 Months as the Outcome Variable

<table>
<thead>
<tr>
<th></th>
<th>3 Months (N=68)*</th>
<th>12 Months (N=69)+</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEM</td>
<td>11.24 1.88 67.31</td>
<td>0.008 4.19 0.46 37.84</td>
</tr>
<tr>
<td>Age</td>
<td>0.85 0.75 0.95</td>
<td>0.005 0.74 0.60 0.91</td>
</tr>
<tr>
<td>Sex</td>
<td>1.33 0.29 6.06</td>
<td>0.710 14.56 1.62 130.88</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.71 0.56 0.90</td>
<td>0.005 0.62 0.43 0.89</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>0.88 0.33 2.38 0.808</td>
<td>0.51 0.16 1.63 0.257</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.43 0.06 2.83</td>
<td>0.379 0.06 0.89 0.041</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OR indicates odds ratio.</th>
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<tbody>
<tr>
<td>*Eleven patients who died were included by assigning a Barthel score of 0; 3 survivors had missing data.</td>
</tr>
<tr>
<td>†Seventeen patients who died were included by assigning a Barthel score of 0; 2 survivors had missing data.</td>
</tr>
</tbody>
</table>

### Figure 2. Number of days to walking 50 m unassisted in VEM and SC groups, adjusted for age, sex, stroke severity (NIHSS), premorbid mRS, and diabetes (N=71). Note: Of those patients who returned to walk in the 12 months after stroke, 142 days was the longest time taken.
associated with bed rest and thus made walking 50 m more difficult. Muscle loss and deterioration in cardiorespiratory function that the increased physical activity served to minimize the likelihood of milder stroke patients being discharged from acute care directly to home rather than to a rehabilitation facility. Our data support this possibility: despite the VEM group having more patients with moderate to severe strokes than the SC group, length of stay in the acute care hospital was shorter for VEM than for SC patients (median 6 vs 7 days), and they were more likely to be discharged directly to home (32% vs 24%). The study by Indredavik et al, in which a shorter time to start of mobilization was the most important factor associated with discharge to home, also supports this idea. A potential explanation for the faster return to walking is that motor performance was improved by earlier and more frequent out-of-bed experiences. It is also possible that the increased physical activity served to minimize the muscle loss and deterioration in cardiorespiratory function associated with bed rest and thus made walking 50 m unassisted less demanding. A further possibility is that self-efficacy was enhanced; that is, the early sessions of mobilization constituted “mastery experiences” that gave the patient increased confidence in his or her own ability to walk.

Our hypothesis that patients exposed to the intervention would have better functional independence than controls at 3 months was supported by the findings from the multiple regression analyses, whereby more VEM patients were independent in ADLs (Barthel Index) and motor function (Rivermead Motor Assessment) than SC patients. Taken together with the walking findings, this indicates that providing earlier and more intensive mobilization after stroke can accelerate the recovery of meaningful physical outcomes. At 12 months, VEM patients remained more independent in motor function than controls, but there was no significant group difference for independence in ADLs. Previous studies have demonstrated that in the longer term, stroke patients who have not received augmented training eventually achieve the same level of function as those who have. It should be noted that our study was not powered to detect changes in functional outcomes in response to the addition of an early mobilization program. As Tables 3 and 4 show, the confidence intervals around the effect of intervention group were wide, and whether these promising findings are confirmed in the larger phase III study (currently underway) remains to be seen.

Age and stroke severity strongly influenced recovery as measured by the Barthel and Rivermead at both 3 and 12 months after stroke, with younger patients and those with less severe stroke achieving greater functional independence. This is consistent with previous findings. The negative influence of diabetes on functional independence found with walking recovery and the Barthel Index at 12 months also has precedent.

As outcome measures in a research context, the Barthel Index and Rivermead Motor Assessment are not perfect. They are brief, ordinal scales that produce data that are not normally distributed, with ceiling effects a particular issue for the Barthel. It is possible that differences in independence in ADLs between groups were present at 12 months in the current study but that a ceiling effect in the Barthel data precluded their detection. More than half of the surviving patients were at ceiling on the Barthel scale (20/20) at 12 months after stroke. The weakness of the Barthel in discriminating between people at moderate versus high levels of independence after stroke.

Table 4. Multivariable Binary Logistic Regressions, With Independence in Motor Function (Rivermead=10–13 vs Rivermead=0–9) at 3 and 12 Months as the Outcome Variable

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEM</td>
<td>8.21</td>
<td>1.00 67.64</td>
<td>0.050</td>
<td>9.62</td>
<td>1.34 68.83</td>
</tr>
<tr>
<td>Age</td>
<td>0.90</td>
<td>0.81 1.00</td>
<td>0.046</td>
<td>0.88</td>
<td>0.78 0.98</td>
</tr>
<tr>
<td>Sex</td>
<td>1.52</td>
<td>0.27 8.67</td>
<td>0.635</td>
<td>4.44</td>
<td>0.83 23.65</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.66</td>
<td>0.54 0.82</td>
<td>&lt;0.001</td>
<td>0.71</td>
<td>0.59 0.85</td>
</tr>
<tr>
<td>Premorbid</td>
<td>0.66</td>
<td>0.27 1.62</td>
<td>0.361</td>
<td>0.44</td>
<td>0.18 1.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.71</td>
<td>0.08 6.38</td>
<td>0.761</td>
<td>0.13</td>
<td>0.02 1.07</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

Eleven patients who died were included by assigning a Rivermead score of 0; 2 survivors had missing data.

Seventeen patients who died were included by assigning a Rivermead score of 0; 2 survivors had missing data.

Any intervention that accelerates functional recovery is important both to stroke survivors and clinicians. This study provides novel evidence that earlier and more intensive mobilization in the acute phase of stroke can accelerate recovery of walking and functional independence. The findings from AVERT phase III will provide greater certainty regarding the efficacy of VEM in the recovery of physical independence after stroke.

Acknowledgments

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Disclosures

None.

References

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Background and Objectives: Early mobilization and more intensive rehabilitation interventions after stroke are associated with improved independent walking in the subacute phase. However, it is unknown whether very early mobilization after stroke, defined as mobilization within the first 24 hours after stroke, results in faster recovery of independent walking.

Methods: A Very Early Rehabilitation Trial (AVERT), a Phase II randomized controlled trial, was conducted to assess the effectiveness of very early rehabilitation intervention after stroke. Patients were randomly assigned to receive either very early or standard rehabilitation intervention. The primary outcome was time to 50-meter walk. Secondary outcomes included Barthel Index and Rivermead Motor Assessment scores at 3 and 12 months after stroke.

Results: Among the 71 enrolled patients, the very early mobilization group showed a statistically significant reduction in time to achieve independent walking compared to the standard rehabilitation group (median time of 3.5 days vs. 7.0 days; p = 0.032).

Conclusion: Very early mobilization after stroke may be a fast-track approach to recovery and may be associated with improved functional outcomes.
示，卒中后短时间内开始活动是与出院直接回家相关的因素之一。我们发现，卒中后第一周常缺少躯体活动，我们认为引入更早的、更密集的活动可以为卒中恢复提供良好的机会。在比较超早期、密集活动（very early and intense mobilization，VEM）和标准卒中单元护理（standard stroke unit care，SC）的 II 期临床试验中，这项干预措施的安全性和有效性研究是主要结局指标。本文中，我们将报告与行走恢复和 ADLs（日常活动）独立性相关的结果。我们假定 VEM 组患者将比 SC 组患者更早的独立行走。我们也假定 VEM 组患者将比 SC 组患者在卒中后 3 个月和 12 个月获得更好的功能上的独立（通过 Barthel 指数和 Rivermead 运动功能评分来测量）。

**方法**

**研究设计**

II 期超早期康复试验（A Very Early Rehabilitation Trial，A VERT）是一项前瞻性、随机对照临床试验，采用盲法分组、盲法结果评估和意向治疗分析。研究机构是澳大利亚墨尔本的两家大医院的急性卒中单元。获得了伦理批准。具体方法在其他文章中已详细报告，将在下一段中简要总结。

**研究人群**

入组标准：(1)≥18 岁；(2) 满意的生理条件（收缩压：120-220 mmHg，心率：40-100 bpm，氧饱和度：>92%，体温：<38.5℃）；(3) 首发或复发卒中，可以在症状发生 24 小时内随机化。排除标准：发病前改良 Rankin 评分 (mRS) 3-5 提示残疾，或在进入卒中单元或监护室后第一小时内恶化、合并进展的神经系统疾病、急性冠脉综合征、严重的心力衰竭、影响活动的下肢骨折或者需要姑息治疗。

**研究步骤**

在讨论知情同意时，告知患者他将会获得两种不同的康复方式中的一种。采用计算机生成、封闭随机化程序和密封的不透明信封，将患者分到 VEM 组或 SC 组。根据医院和卒中严重程度对随机化进行分层来减少组间严重程度的不平衡性，其中卒中严重程度根据 NIHSS 来判定（轻度：0-7 分，中度：8-16 分，重度 >16 分）。在 VEM 组患者在随机化后，尽可能早的开始活动，来达到卒中后 24 小时内开始第一次活动的目标。VEM 组患者也获得额外的干预，即将以前提到的标准护理 “活动的剂量” 增加一倍，以达到帮助患者每天站立和下床至少两次的目标。VEM 组患者前三次活动时，需监测其血压、心率、氧饱和度及体温。在整个研究过程中，监测 VEM 组是否受到标准护理的 “污染”。

**干预措施**

VEM 和 SC 组均在卒中单元中获得病房治疗师和护理者的标准护理。VEM 组患者在随机化后，尽可能早的开始活动，来达到卒中后 24 小时内开始第一次活动的目标。VEM 组患者也获得额外的干预，即将以前提到的标准护理 “活动的剂量” 增加一倍，以达到帮助患者每天站立和下床至少两次的目标。由经过训练的卒中单元的护士和物理治疗师组成的团队来完成 VEM。时间为卒中后最初的 14 天或直至出院（选择两者中比较早的）。两组患者的治疗类型和剂量均记录入掌上电脑中。人工辅助患者活动时，始终给予专业的健康和安全措施。在 VEM 组患者前三次活动时，需监测其血压、心率、氧饱和度及体温。在整个研究过程中，监测 VEM 组是否受到标准护理的 “污染”。

**基线评估**

基线评估包括年龄、性别、牛津郡卒中分型（OWAS）、卒中严重程度 (根据 NIHSS 确定)、糖尿病及其他卒中危险因素、卒中前的生活方式、卒中前功能分级 (根据 mRS 确定)。应用急性卒中活动性评分 (the mobility scale for acute stroke，MSAS) 来确定患者在床上的活动能力、坐起、行走 10 米等方面受限的情况，同时利用从该评分获得的信息来指导 VEM 干预措施的级别。

**结局测量**

分别在卒中后 7 天、14 天、3 个月、6 个月及 12 个月时进行盲法评估。此次数据分类时，最感兴趣的结局指标是至能够行走 50 米的时间。其定义是患者第一次不需人为帮助而行走 50 米距卒中发病的天数，50 米是功能独立性测量 (Functional Independence Measure，FIM) 中行走项目判定所用的距离，而且常常在病房内划出 50 米的界限。为了降低与同时需要监督 (FIM 5 分) 和助行器 (FIM 6 分) 相关的主观性，我们将行走定义为 “不需要人为帮助而能够连续行走 50 米 ( 可以使用助步器 )”。物理治疗师负责完成行走 50 米的测定。其他的结局指标是卒中后 3 个月和 24 个月时的 Barthel 指数和 Rivermead 运动功能评分。Barthel 指数是卒中研究中有效的、可靠的评价 ADLs 的指标，它用来评价 10 项日常活动的独立性；总分是 20 分，分数越高，独立性越好。根据每次 Barthel 指数评分将患者分为 ADLs 独立组 (20 分) 和非独立组 (0-19 分)。应用 Rivermead 运动功能评分来评价运动活动，它包含 13 个项目，其可靠性也已得
到证实[23,24]。它同时包含容易的和困难的项目,第
一个项目测试无支持时坐起的能力,其他项目测试
转移、室内行走、室外行走、跑和原地跳跃的能力。
进行三次测试,记录最好的一次,
0 分表示患者不
能独立完成任何一项活动,
13 分提示患者能够独立
完成所有活动。将患者分为运动活动受损组
(0-9 分)
和未受损组 (10-13 分), 该分界点与有临床意义的
户外行走能力一致。

统计分析
70 例的样本量,足够以本研究的主要安全性结
局测量指标 (卒中后 3 个月时的死亡)
来检查本研究的
安全性[14]。虽然本研究探测不同躯体活动结局的
效力不强,但是可进行可行性分析,评估结局测量
指标的表现和应用效能。
因为在卒中后最初的 12 个月内,有 1/3 的患者
死亡,所以分析时必须考虑到死亡造成的数据缺失。

因在卒中后最初的 12 个月内,有 1/3 的患者
死亡,所以分析时必须考虑到死亡造成的数据缺失。

至能行走的天数
记录卒中发病与独立行走 50 米之间的天数。对
重要的影响预后的变量 (年龄、性别、NIHSS、卒中
前 mRS 和糖尿病) 进行校正后, 进行 Cox 回归分析。

**Barthel 指数**

对 Barthel 指数进行 Mann-Whitney U 检验, 评价其组间差异。根据 Barthel 指数将患者分为 ADLs 独立组和非独立组, 进行 Fisher's 确切概率检验评价组间差异。将 Barthel 指数作为二分类结局变量, 对组别 (VEM 组或 SC 组)、年龄、性别、NIHSS、卒中前 mRS、糖尿病进行多变量 logistic 回归分析, 评价其对 ADLs 独立性的影响。

**Rivermead 运动功能评分**

对 Rivermead 运动功能评分进行 Mann-Whitney U 检验, 分析其组间差异。根据 Rivermead 运动功能评分将患者分为运动活动受损组和未受损组, 进行 Fisher's 确切概率检验, 评价组间差异。用与 Barthel 指数相同的方法, 对 Rivermead 运动功能评分进行多变量 logistic 回归分析。
表4 多变量二元Logistic回归分析，以3个月和12个月时的运动功能独立性 (Rivermead运动功能评分 = 10-13 vs Rivermead运动功能评分 =0-9) 作为結果变量

<table>
<thead>
<tr>
<th></th>
<th>3个月 (N=68)*</th>
<th>12个月 (N=69)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95%CI P</td>
<td>OR 95%CI P</td>
</tr>
<tr>
<td>VEM</td>
<td>8.21 1.00 67.64 0.050</td>
<td>9.62 1.34 68.83 0.024</td>
</tr>
<tr>
<td>年龄</td>
<td>0.90 0.81 1.00 0.046</td>
<td>0.88 0.78 0.98 0.024</td>
</tr>
<tr>
<td>性别</td>
<td>1.52 0.27 8.67 0.635</td>
<td>4.44 0.83 23.65 0.081</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.66 0.54 0.82 0.001</td>
<td>0.71 0.59 0.85 0.001</td>
</tr>
<tr>
<td>发病前</td>
<td>0.66 0.27 1.62 0.361</td>
<td>0.44 0.18 1.05 0.065</td>
</tr>
<tr>
<td>糖尿病</td>
<td>0.71 0.08 6.38 0.761</td>
<td>0.13 0.02 1.07 0.058</td>
</tr>
</tbody>
</table>

OR，比值比。
* 包括了11例死亡患者、Rivermead运动功能评分定为0分；2例存活者有数据缺失。
† 包括了17例死亡患者、Rivermead运动功能评分定为0分；2例存活者有数据缺失。

Barthel指数

3个月时21%的存活者由代理人回答问题，12个月时17%由代理人回答(主要是因为患者交流有困难)。Barthel指数的分布呈双峰型，多数患者集中在最低分或最高分。3个月时VEM组Barthel指数得分高于SC组(VEM组中位分18.5，IQR，2.0-20.0；SC组中位分16.5，IQR，9.0-20.0)，但是差异无统计学意义(P=0.713)。3个月时，47%的VEM组患者获得了好的(根据Barthel指数确定)的结局，28%的SC组患者获得了好的结局(P=0.136)。12个月时两组患者的Barthel指数得分无显著差异，VEM组与SC组患者均有39%获得了好的结局(VEM组中位分18.0，IQR，0.0-20.0；SC组中位分18.0，IQR，7.0-20.0)。多元回归分析显示，3个月时好的Barthel指数结局与VME、入组时较轻的卒中(NIHSS)、年龄轻独立相关。12个月时好的Barthel指数结局与较轻的卒中、年龄轻、男性、无糖尿病独立相关，但是与VEM无明显相关(表3)。只分析存活患者所得的结果相似(数据未显示)。

Rivermead运动功能评分

VEM组与SC组3个月时的Rivermead运动功能评分相似(VEM组中位分10.0，IQR，0.5-11.0；SC组中位分10.0，IQR，3.0-11.0；P=0.883)。3个月时，62%(23/37)的VEM组患者获得了好的(根据Rivermead运动功能评分确定)的结局，56%(18/32)的SC组患者获得了好的结局(P=0.633)。12个月时两组患者的Rivermead运动功能评分无显著差异，53%的VEM组患者获得了好的结局(中位分10.0，IQR，0.0-11.0)，45%的SC组患者获得了好的结局(中位分9.0，IQR，1.0-11.0)。

讨论

本研究最重要的发现是同时接受超早期活动的患者比仅获得卒中单元护理的患者能够更快的恢复独立行走。此发现的主要临床意义是患者更快的恢复行走，增加了患者从急性治疗中直接出院回家的可能性。虽然VEM组较SC组有更多的中至重度卒中患者，但是VEM组患者在急性治疗医院中的时间比SC组短(中位时间分别为6天和7天)，而且更多的VEM组患者直接出院回家(32% vs 24%)。

Indredavik 等[12]的研究显示短时间内开始活动是影响出院回家的最重要的因素，也支持我们的观点。更快的恢复行走的可能原因是更早和更频繁的下床活动改善了运动机能；另一个可能的原因是，增加的躯体活动使肌肉萎缩最小化，使与卧床相关的心肺功能恶化最小化[25]，从而使独立行走30米不费力；还可能是因为早期活动增强了患者的生活质量，从而支持了患者的“控制经验”，从而增强了其对自我行走能力的信心[26,27]。

多元回归分析显示更多的VEM组患者在ADLs方面的Barthel指数和运动功能(Rivermead运动功能评分)上具有独立性，从而支持了我们的设想，即3个月时干预组患者比对照组有更高的功能独立性。结合恢复行走方面的发现，提示我们卒中后更早的和更密集的活动可以加快有意义的躯体活动的恢复。12个月时，在运动功能方面，VEM组较对照组仍然更加独立，但是两组间ADLs独立性方面无显著差异。既往的研究显示，在远期，未受增强训练的卒中患者与接受增强训练的患者最终获得相同
等级的功能[3]。应该注意的是，我们的研究探测早期活动导致的功能结局变化的效力不强。如表3、4所示，干预措施的效果的置信区间较宽，需要在更大规模的III期研究(正在进行中)[29]进一步确定这些发现。

年龄和卒中严重程度对3个月和6个月时的卒中结局(根据Barthel指数和Rivermead运动功能评分确定)有很大影响，年轻患者和卒中程度轻的患者将获得更多的功能独立性。该发现与以往研究结果一致[7-9]。既往也有研究显示糖尿病对行走恢复及12个月时的Barthel指数有负面的影响[8,10]。

Barthel指数和Rivermead运动功能评分并不是完美的研究结果预测指标。它们是简短的等级评分，评分结果不呈正态分布，而且Barthel指数有天花板效应。可能12个月时两组患者在ADLs独立性上有差异，而Barthel指数的天花板效应影响了这些差异的探测。12个月时，超过一半的存活者达到了Barthel指数评分的天花板(即获得了满分20分)。Barthel指数在区分有中等和高水平功能的患者上的劣势已得到充分证实[29]。另外，Barthel指数和Rivermead运动功能评分都没有包含死亡情况(而mRS包含了死亡)。与许多发表的康复研究相比，本研究分析躯体活动结局时并未排除死亡。而为了避免高估死亡患者的恢复，我们将死亡者的这两项评分都定为了0分。考虑到上述情况，需要将这两项评分结果进行二分法分析，以免违反统计假设。二分法的后果是降低了测量的敏感性。但是这种策略在康复领域(无论是临床实践还是研究中)被广泛应用且欣然接受，所以我们选择了这种结局测量方法。

任何能加速卒中后期功能恢复的措施对卒中患者和医生都很重要。本研究提供了新的证据：在卒中急性期，更早和更密集的活动可以加速行走功能独立性的恢复。AVERTIII的发现将更确定VEM对卒中后躯体独立性恢复的效力。

参考文献


