AVERT Trial Debate: 
Implications for Practice
Have we “AVERT”ed the real message?

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Case Scenario

• Mr. M., 80 yo male, previously independent with sudden R sided weakness, difficulties with standing balance, and unable to walk without assist of wife.
• Arrives in emergency, CT scan confirms stroke; NIH Stroke Scale of 10 (Moderately severe)
• Transferred to the Acute Stroke Unit. You are going to see Mr. M. to assess and begin treatment as appropriate.
• It is now 3:30 pm, it’s been 14 hours since stroke onset.
• Would you practice standing and walking with Mr. M today?  
• Yes? No? Maybe? What else would you like to know?

Objectives

• Review study design and results  
• Discuss the interpretation and in particular in the context of other relevant literature  
• Consider the implications for your day to day acute stroke care practice

• What we need from you – to give us your thoughts, questions, concerns in each of these areas!
Background

- Arguments for early mobilisation improving outcomes?
  - Bed rest negatively affects cardiovascular, musculoskeletal, respiratory and immune systems
  - Complications occur related to immobility (e.g. pressure sores)
  - Neuroplasticity may be potentiated, especially if there is a narrow window

- Arguments against early mobilisation improving outcomes?
  - Increasing blood pressure early might cause further neuro damage
  - Upright head position might reduce cerebral blood flow, especially important to the penumbral area
  - Increased risk of falls

What is very early mobilisation?

- Started within 24 hours after stroke
- Continued to occur "frequently" thereafter

Hypothesis

More intensive, early out-of-bed activity would:
- Improve functional outcomes at 3 months (modified Rankin)
- Accelerate walking recovery (independent 50 m walk, unassisted walking)
- Reduce immobility-related complications
- Improves quality of life at 12 months (Assessment of Quality of Life)
- With no increase in neurological complications

Study methods

- Pragmatic
- Single-blind (intervention staff, participants and evaluators)
- Randomised controlled trial
- Multicenter: 56 sites in Australia, New Zealand, Malaysia, Singapore, UK
- Inclusion
  - 18 years or older
  - Confirmed stroke, admitted within 24 hours
- Exclusion
  - Significant premorbid disability
  - Significant illness, very high or low BP or heart rate
Interventions

• Usual care
• Very Early Mobilisation
  • Begin within 24 hr of stroke
  • Focus on sitting, standing, walking
  • At least three additional out-of-bed sessions compared to usual care
  • 14 days or until discharge

Baseline characteristics
Intervention summary

<table>
<thead>
<tr>
<th>Primary Outcome: Functional Improvement</th>
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<tbody>
<tr>
<td>Rank</td>
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<tr>
<td>0</td>
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Primary outcome by Rankin category

![Graph showing proportion of patients with various outcomes across different Rankin categories.](image)
Primary outcome by key subgroups

Safety

<table>
<thead>
<tr>
<th></th>
<th>Very early mobilization (n=1654)</th>
<th>Usual care (n=8060)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>80/148</td>
<td>71/340</td>
<td>1.34 (0.69-2.59)</td>
<td>0.113</td>
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</tbody>
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Author’s Conclusions

The very early, higher dose out of bed activity protocol reduced the odds of favourable outcome, without accelerating walking recovery or reducing immobility-related SAEs

There is better may not apply in the first few days after stroke

There were low rates of death or serious adverse events, with non-significant differences that suggests signals of harm in ICH and severe stroke

Treatment dose versus benefits/harms warrants further exploration
Can we apply the main findings of the AVERT trial?

If yes....How??

AVERT Trial is impressive, but not perfect:
Potential threats to validity

Who was and was not enrolled?
• 2104 enrolled out of 25237 patients screened (Only 8.3%)
• Female patients less likely to be enrolled (OR 0.67, p<.01)
• Older patients less likely to be enrolled (0.99, p<.01)

Where was study conducted?
Urban organized stroke units/beds in Australasia and UK

When was study conducted?
• Between 2006 – 2014
• What other system changes have occurred during this time?


What elements of early mobility practice affect outcomes?
What elements of early mobility practice affect outcomes?

Secondary analysis of pooled data from all participants (n=2104)

Dose-response analysis of:
- Time to first mobilization
- Amount of time spent in mobility practice
- Frequency of mobility practice sessions

What was Very Early Mobility practice?

VEM: out-of-bed, mobility-related practice
- Earlier <24 hours post-onset
- More frequent (≥ 3 additional episodes),
- More time spent in out-of-bed activity

Note: Passive sitting in chair not counted

Target activities: Active sitting (e.g. edge of bed), standing, walking
Two bouts of mobility interrupted by >5 min rest = 2 episodes
Discouraged activity episodes > 50 minutes

96% mobilized within 48 hrs of stroke
75% mobilized within 24 hrs of stroke
Dose-response analysis

- Evaluated the independent impact of each of the mobility variables (e.g. Time to first mobility, Frequency, Amount [minutes])
- Adjusted for age, and initial stroke severity (NIHSS)
- Time to first mobility also adjusted for Frequency, and Amount
- Frequency also adjusted for Time to first mobility and Amount
- Amount also adjusted for Time to first mobility and Frequency

Dose-response analysis: Age and baseline stroke severity

- Age and baseline stroke severity were strongest predictors of favourable outcome at 3 months
- Younger patients (≤76.3 years) with low NIHSS score (≤7.5 out of 42) had a high probability of a favourable outcome at 3 months (78.2%)
  - That is, 8 out of 10 younger patients with milder stroke symptoms recovered with mild stroke disability, independent of timing, duration and frequency of mobility training

Dose-response analysis: Time to first mobility

- Greater time to first mobilization associated with reduced odds of favourable outcome (0.99, 0.98–1.00, p=0.036)
- For 2 patients of similar age and stroke severity, receiving a similar frequency and amount of mobility, the patient who starts mobilization earlier has improved odds of a favourable outcome
Dose-response analysis: Frequency

Keeping time to first mobilization and amount constant, increasing the frequency of sessions by 1 session improved the odds of favourable outcomes by 13% (95% CI 9-18%, p<0.001), and improved odds of walking 50 m unassisted by 66% (95% CI 53-80, p<0.001)

Dose-response analysis: Amount (minutes)

Keeping time to first mobilization, and frequency constant, every extra 5 minutes of out-of-bed activity per day reduced the odds of a favourable outcome (OR 0.94 [0.91-0.97], and achieving indep walking for 50 m (OR 0.85[0.81-0.89])

Dose-response Analysis: Death and SAEs

• Increasing frequency by 1 session reduced the odds of death by 22%
• Increasing time per day by 5 min. reduced odds of non-fatal serious adverse events by 4%
Dose-response analysis: Take-away

- Mobilization within 24 hours of stroke onset is associated with improved outcomes
- Must consider the timing, frequency and amount of therapy – not just amount
- Frequency of intervention seems to be an important driver of outcome
- Early after stroke, teams must be cautious about increasing amount of time in mobility practice, particularly without distributing over greater number of episodes

Dose-response: Regression analysis

- Method of exploring the contribution of the dose-characteristic variables (Frequency and Amount) on outcomes

Dose-response: Regression analysis

2 patients: Both between 76-86 yrs, NIHSS > 4.5
Both receive > 13.5 minutes per day of mobility
For the same amount of total mobility time, the patient who has frequency of > 10 sessions is more likely to do well, compared to those who have < 10 sessions
Do the results make sense?

• Physical Activity Research
  • Shorter bouts of physical activity (10 minute bouts) throughout your day may deliver greater cardiovascular benefit than a single bolus of exercise – and being sedentary the rest of the day.

• Motor learning
  • Distributed practice of motor skills (interrupting practice with rests or other activity) better than Massed practice – allows consolidation, and retention of learning

• Impact of high intensity practice on other biological processes happening in the initial period after stroke? Needs further study

What do the guidelines say?

“...Despite that early mobilization after stroke is recommended in many clinical practice guidelines worldwide, the findings from the AVERT trial demonstrate that it may be associated with a reduction in favourable outcomes and challenge this pre-existing notion.”

Canadian Best Recommendations 2016, Delivery of Inpatient Rehabilitation

What do the guidelines say?

Frequent, out-of-bed activity in the very early time frame (within 24 h of stroke onset) is not recommended. Mobilization may be reasonable for some patients with acute stroke in the very early time frame and clinical judgment should be used.

All patients admitted to hospital with acute stroke should start to be mobilized early (between 24 h and 48 h of stroke onset) if there are no contraindications.

Contraindications to early mobilization include, but are not restricted to, patients who have had an arterial puncture for an interventional procedure, unstable medical conditions, low oxygen saturation, and lower limb fracture or injury.

(Note: rPA was not a contraindication in the AVERT study)
Revisiting Mr. M.

Would you get Mr. M up and walking? 
For how long? How often? How/who will you do this?

Is this a change in your practice? 
What strategies could help implement these findings?

Final thoughts and questions