

THE UNIVERSITY OF TENNESSEE  
HEALTH SCIENCE CENTER

## To Rest or Mobilize...Evidence Based Recommendations for Mobility Following Acute Ischemic Stroke

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## Disclosures

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Speakers Bureaus:  
Genentech  
Chiesi

Research:  
Principle Investigator, Heads Down  
Principle Investigator, ZODIAC

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## History of Early Mobilization

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First discussed at a conference on stroke care in Sweden in the 1980's

In the 1990's Indredavik and colleagues reported a decrease in death and disability when early rehabilitation was compared to general care

AVERT was the first multisite, international randomized controlled trial conducted; beginning in 2004, through 2014 (published 2015)




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## How is Early Mobilization Defined?



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## Background

Recent nursing initiatives encourage early mobilization of neurocritical care patients, but whether this intervention is efficacious and safe in neurocritical care remains unknown, AND whether this can be safely generalized to acute stroke is debatable.



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### To Rest or Mobilize...

#### When to Start Early Mobilization in Acute Stroke:

##### A Systematic Review

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### Methods

Literature search was performed

- Medline, SCOPUS, Cochrane Center Register of Controlled Trials

“Very Early Mobility Intervention” = within 24 hours

Patient population exclusively acute stroke patients

Primary efficacy outcome:

- Neurologic disability reduction
- Improved functional outcomes

Primary safety outcome was neurologic deterioration

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### Methods

Studies were critically reviewed for inclusion by 3 separate investigators

- Prospective randomized outcome-blinded evaluation (PROBE) designs were retained

Findings were synthesized and a GRADE criterion was assigned

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### GRADE Criteria

<b>High</b>	<ul style="list-style-type: none"><li>• Randomized trials</li><li>• Double-upgraded observational studies</li></ul>
<b>Moderate</b>	<ul style="list-style-type: none"><li>• Downgraded randomized trials</li><li>• Upgraded observational studies</li></ul>
<b>Low</b>	<ul style="list-style-type: none"><li>• Double-downgraded randomized trials</li><li>• Observational studies</li></ul>
<b>Very Low</b>	<ul style="list-style-type: none"><li>• Triple-downgraded randomized trials</li><li>• Downgraded observational studies</li><li>• Case series/case reports</li></ul>

handbook.cochrane.org

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## Results

12 papers focused on early mobilization in acute stroke were identified

- 6 observational studies were excluded
- 1 study was excluded due to an ambiguous population
- 3 studies were excluded due to first initial mobilization out of bed occurring greater than 24 hours after admission

Two prospective randomized outcome blinded evaluation (PROBE) studies were retained

- Total 2160 patients

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## Retained Studies

Publications	Methods	Main Findings
Sundseth A, Thommessen B, Ronning DM. Outcome after mobilization within 24 hours of acute stroke: A randomized controlled trial. <i>Stroke</i> ; 2012;43(9):2389-2394.	PROBE design	<u>Very early mobilization (VEM) patients showed a trend towards poor outcome (OR=2.7), death (OR=5.26), or dependency (OR=1.25); p=ns. (n=56).</u>
The AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. <i>Lancet</i> . 2015;386:46-55.	PROBE design	<u>Fewer VEM patients had favorable outcome (46%; n=480), compared to usual rested care (50%; n=525; adjusted OR=0.73; p=0.004). Death associated with neurologic deterioration or recurrent stroke in the VEM group totaled 42, compared to 26 in the usual care group; pneumonia as a cause of death occurred in 19 VEM vs. 15 usual care patients. Stroke progression occurred in 72 VEM vs. 56 usual care patients. (n=2104).</u>

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## Results

Slower mobilization occurring beyond the first 24 hours was associated with higher favorable outcome (mRS 0-2) at 90 days

Very early mobilization (within first 24 hours) was associated with a number needed to harm of 25




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## Comparison Studies

Paper	Methods	Main Findings
Lynch E, Hillier S, Cadihac D. When should physical rehabilitation commence after stroke: A systematic review. <i>International Journal of Stroke</i> . 2014;9(4):468-478.	Systematic review and meta-analysis	Meta-analysis of 3 RCTs: Commencing rehabilitation within 24 hours, compared to after 48 hours, showed a trend toward greater mortality (OR 2.58; p=0.06; m=159). Whereas cohort studies provided conflicting findings.
Stokelj F, Musho Ibeh S, Granato A, Serillo G, Pizzolato G, Chioda Grandi F. Very early versus delayed mobilisation after stroke. <i>Neuroepidemiology</i> . 2010;35:163-164.	Cochrane systematic review of randomized controlled trials.	No difference in death or poor outcome at 3 months, or death or dependency at 3 months. <u>8 deaths with VEM compared to 3 deaths with usual rested care</u> at 3 months (p=ns). (n=69)

**Numerous studies in cardiac patients with coronary insufficiency demonstrate superior outcomes with a more rested approach immediately after admission!**

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## Systematic Review Conclusions

In acute stroke, evidence supports a rested approach to care within the first 24 hours of hospitalization

- GRADE: Strong recommendation, high quality of evidence

Similar to acute MI, vascular insufficiency in acute stroke likely warrants a more guarded approach to mobility

Additional studies are warranted to determine the optimal "dose" and "timing" of exercise/mobility in acute stroke, and whether this differs by stroke subtype and mechanism

Patients recruited to early mobility trials should undergo informed consent that clearly defines potential risks to ensure the ethical conduct of research

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## So, what to do now?



Should we slam on the brakes and just leave patients in bed?

If so, for how long?

What about positioning of patients?

Are there differences in what positions may benefit patients?

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## History of Reported Clinical Change and/or Blood Flow Related to Head Positioning

### Worsening in relation to head elevation:

- Toole, JF. *New England Journal of Medicine*. 1968;279(6):307-311
- Caplan LR, Sergay S. *Journal of Neurology, Neurosurgery and Psychiatry*. 1976;39(4):385-391
- Ali LK, Saver JL, Kim D, Starkman S, Ovbiagele B, Buck B, Sanossian N, Vespa P, Jahan R, Duckwiler G, Vinuela F, Liebeskind, D. *Neurology*. 2006;66(5) suppl 2:A159

### Impact on cerebral blood flow:

- Hayashida K, Hirose Y, Kaminaga T, Ishida Y, Imakita S, Takamiya M, Yokota I, Nishimura T. *Journal of Nuclear Medicine*. 1993;34(11):1931-5
- Duchi Y, Nobezawa S, Yoshikawa E, Futatsubashi M, Kanno T, Okada H, Torizuka T, Nakayama T, Tanaka K. *Journal of Cerebral Blood Flow and Metabolism*. 2001;21(9):1058-1066
- Wojner AW, El-Mitwalli A, Alexandrov AV. *Critical Care Nursing Quarterly*. 2002;24(4):57-66
- Wojner-Alexandrov AW, Garami Z, Chernyshev OY, Alexandrov AV. *Neurology*. 2005;64(8):1354-1357
- Durduran T, Zhou C, Yu G, Edlow B, Choe R, Shah Q, Kasner SE, Cucchiara BL, Yodh AG, Greenberg JH, Debra JA. *Stroke*. 2007;38(2):494
- Hunter AJ, Snodgrass SJ, Quain D, Parsons MW, Levi CR. *Physical Therapy*. 2011;91(10):1503-1512

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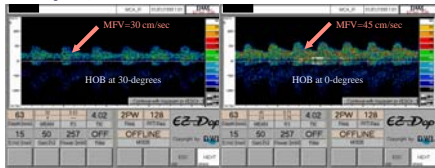
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## Heads Down

Wojner-Alexandrov, AW, Garami, Z, Chernyshev, OY, & Alexandrov AV. (2005). Heads down: Flat head positioning improves blood flow velocities in acute ischemic stroke. *Neurology*, 64(8):1354-1357.

20% increase in mean flow on average in large artery occlusions when HOB lowered from 30-degrees to 0-degrees (effect size for the intervention at three levels = 0.47;  $r = 0.90$  and observed power of 0.99)



18% of subjects demonstrated clinical improvement within 30 minutes of placing the head at 0-degrees flat positioning.

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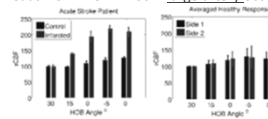
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## Other Key Head Positioning Studies

### UCLA – “Heads Up” Pilot

- Patients with clinical improvement but persisting large artery occlusions deteriorated when the HOB was elevated

### UPenn – “Heads Down” CBF Pilot in large artery occlusions



HOB0E – Incompletely recanalized large artery occlusions demonstrated increased flow with zero-degree positioning

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## However...

These are small studies  
 Limited to large vessel ischemic stroke  
 Primary end point in Heads Down and HOBOE was imaging-related

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## What About Small Vessel Occlusions?

M. Aries et al: HOB positioning does not produce a difference in cerebral blood flow or clinical changes in patients with mild to moderate stroke

W.J. Hicks et al: Patients with small vessel occlusions do not fluctuate clinically in response to HOB positioning; predictors of clinical change were tPA treatment and a finding of large vessel occlusion presenting as a subcortical stroke mimic

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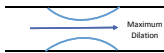
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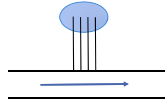
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### Large Artery Stenosis



### Small Artery Occlusion



### Large vs. Small Artery Stroke...Why the Difference?

- |   |   |
|---|---|
| <ol style="list-style-type: none"> <li>1. Vasomotor exhaustion with maximal vasodilation distal to stenosis</li> <li>2. Gravitational force and potentially collateral flow favors blood flow through stenotic segments</li> <li>3. Pressure augmentation "may" be beneficial in select cases</li> </ol> <p>(P1 - P2)/R = Q</p> | <ol style="list-style-type: none"> <li>1. Edema from surrounding infarction mediates clinical fluctuation and limits perforating artery flow; might early mobilization and HOB up be better?</li> <li>2. No evidence that gravitational force, volume or pressure augmentation may change clinical outcome</li> </ol> |
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## Aspiration Safety

Palazzo, P, Brooks, A, James, D, Moore, R, Alexandrov, A.V. & Alexandrov, A.W. Risk of pneumonia associated with zero-degree head positioning in acute ischemic stroke patients treated with intravenous tissue plasminogen activator. *Brain and Behavior*. 2016;6(2):e00425. doi: 10.1002/brb3.425. eCollection 2016 Feb.

### Aspiration pneumonia pilot work:

- Consecutive IV-tPA treated patients were routinely positioned at zero-degrees for the first 24 hours as institutional standard of care
- All patients were kept NPO during the 24 hour zero degree period per institutional protocol
- Pneumonia was defined as hospital acquired pneumonia occurring 48 hours or more after admission and not incubating at time of admission; findings for diagnosis:
  - New or progressive infiltrate on lung imaging & at least 2 of the following:
    - Fever 38 C (100.4 F)
    - Purulent sputum
    - Leukocytosis
    - Decline in oxygenation




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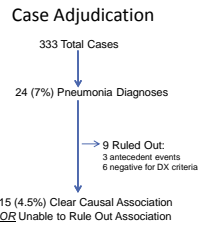
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## Safety questions...

### Aspiration pneumonia pilot work (continued):

- Pneumonia cases were adjudicated by vascular neurology, critical care, pulmonology, and emergency medicine experts to establish consensus on:
  - If the diagnosis of pneumonia met evidence-based criteria
  - Causal association with heads down
- Of the 15 remaining cases, a clear causal association was established in 1 case (0.3%), and possible association was established between zero-degree positioning and pneumonia in 14 cases (4.2%).
- Collectively, these 15 adjudicated cases had similar median admission NIHSS scores to non-pneumonia cases (10 vs. 9; p=ns), but were older (74±15 vs. 64±17 years; mean difference 9.89 years, 95% CI=1.2-18.6; p=0.026).




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## Measuring the Endpoint

**PROXIMAL ENDPOINT – THE INTERVENTION IS BENEFICIAL ONLY IF EARLY IMPROVEMENT OR STABILITY OCCURS**

100% of the data on head positioning are supported by a proximal outcome measure:

- Within minutes of initiation of the intervention
- Blood flow measures
- Clinical outcomes measures

**DISTAL ENDPOINT – THE INTERVENTION IS BENEFICIAL ONLY IF 90 DAY OUTCOME IS IMPROVED**

No data exist to show that early, hyperacute HOB positioning could possibly effect 3 month outcome after stroke

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### 3 Month Outcome & The "Shock" Paradigm

International standard of care for resuscitation during an acute shock event constitutes "rescue" therapy with the head of bed (HOB) positioned at least to zero degrees, as recommended by Holtenberg, to improve blood flow to the brain.

However...

- Does zero-degree positioning constitute "rescue" therapy for shock?
- Could zero-degree positioning, with the provision of other therapies (control of hemorrhage and resuscitation in the case of hemorrhagic shock; diuresis and left ventricular unloading in cardiogenic shock, etc) improve 3 month outcome following an acute shock event?



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### 3 Month Outcome...

Is more likely tied to treatment (reperfusion therapy), NOT a temporary HOB rescue measure

Similar to the management of shock patients, zero-degree HOB positioning might likely be viewed as an *adjunctive measure* that may provide time to get a patient with severe stroke to definitive treatment with thrombolysis and/or endovascular management

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### So.....

Given what we know now, how should a clinical trial be designed to answer the question about acute stroke positioning?

- Hyperacute-phase trial
- Confirmed large artery stroke patients
- No interference with approved standard of care (i.e. alteplase tPA and thrombectomy)
- Exquisite monitoring for patient change (neurologic and pulmonary deterioration [safety], and clinical neurologic stability or improvement [primary endpoint])
- Proximal endpoint measurement
- Stopping rules and separate Data Safety Monitoring Board that will take interim looks at the data to determine the need to stop due to safety or futility

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Cluster randomized outcome-blinded study of head positioning in acute stroke

- All stroke patients were included to determine if head positioning could improve outcomes
- All patients were randomized to either 0° or 30° head of bed (HOB) positioning
- No difference in 90-day mortality or functional outcome between groups
- All patients were included to get out of bed to use the toilet
- High rates of pneumonia in the 30° HOB group, yet the study wasn't stopped due to safety

HeadPost failed to use existing data and a sound physiologic framework to design a study to answer the question, "How should hyperacute large artery ischemic stroke patients be positioned to best support improved blood flow and clinical outcome?"

**No difference in 90 day outcome, but risky due to pneumonia**

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**ZERO DEGREE HEAD POSITIONING IN ACUTE ISCHEMIC STROKE**

A MULTISITE PROSPECTIVE RANDOMIZED OUTCOME-BLINDED EVALUATION (PROBE DESIGN) CLINICAL TRIAL OF HEAD POSITIONING IN HYPERACUTE LARGE ARTERY ISCHEMIC STROKE

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**Specific Aims**

Primary Aim:

- To identify if use of 0° HOB positioning is associated with clinical stability in hyperacute ischemic stroke.
- Hypothesis: Patients with large vessel occlusions placed in a 0° HOB position, (superiority hypothesis), will experience less early neurologic deterioration within the first 24 hours, than those in the 30° HOB elevation group*

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## Secondary Aims

### Time-Associated Benefit:

- To understand the dynamic change in NIHSS over 24 hours, at discharge (or day 7), and 90 days.
- Hypothesis: The neurological effect of 0°-HOB will occur early following implementation.

### Safety:

- To confirm the safety of 0°-HOB positioning in AIS patients.
- Hypothesis: Positioning the patient at 0°-HOB is safe.

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## Inclusion Criteria

Age  $\geq$  18 years

Diagnosis of AIS made by clinical exam and noncontrast CT or MRI

Arrival to the hospital within 12 hours of symptom onset, with ability to start protocol before 12 hours

Non-contrast CT negative for hemorrhage

Routine CTA or MRI with MRA shows evidence of large artery occlusion

Pre-stroke mRS  $\leq$  1

All responses must be affirmative

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## Exclusion Criteria

Pregnancy or suspicion of pregnancy

Non-English speaking

Anticipated palliative care referral

Evidence or suspicion of prehospital vomiting, or vomiting at any time prior to consent

Evolving malignant infarction on admission noncontrast CT (or MRI)

Mechanical thrombectomy started > 6 hours from symptom onset

Need for emergent intubation with mechanical ventilation, or non-invasive ventilatory support with either bi-level positive airway pressure (BiPAP) or continuous positive airway pressure

Inability to tolerate zero-degree positioning due to congestive heart failure, preexisting pneumonia, chronic obstructive pulmonary disease, or other medical condition

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## Exclusion Criteria, continued

- History of sleep disordered breathing or obstructive sleep apnea
- Abnormal breath sounds on admission assessment
- Pulse oximetry less than 97%
- Chest radiograph or clinical findings positive for significant pleural effusion, pulmonary edema, pneumonia, or other pulmonary condition that may confound determination of protocol safety
- Lack of a telephone and/or permanent address
- Enrollment in another clinical trial
- Any medical, psychological, cognitive, social or legal condition that would interfere with informed consent and/or capacity to comply with all study requirements, including the necessary time commitment and 3 month telephone follow-up

All responses must be negative

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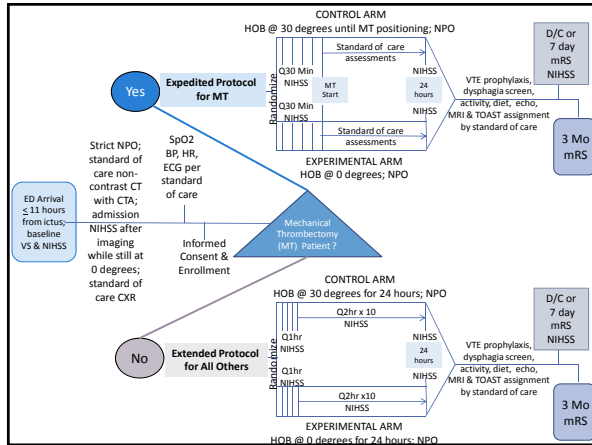
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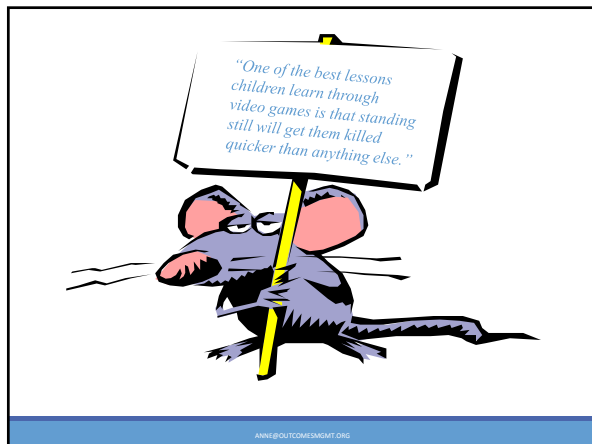
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## Summary

We do know that:

- Early aggressive rehabilitation (within the first 24 hours of an acute stroke event) is UNSAFE!
- Allowing patients placed at zero degrees to eat/drink is UNSAFE, whereas maintaining NPO with side-lying position in these patients is SAFE!
- 90 day (3 month) outcomes are not impacted by a HOB rescue maneuver

We do not know:

- When to initiate rehabilitation in acute stroke patients
- What dose of rehabilitation should be administered to acute stroke patients
- Whether HOB positioning at zero degrees is important to maintain stability and/or promote improvement in hyperacute large artery stroke
- Whether HOB positioning could be important in other types of acute stroke patients

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