SSVQ
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Hôpital général juif
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Top 3, Étude
AVERT

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Conflits d'intérêts

- Aucun

Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial

The AVERT Trial Collaboration group*

- Lancet 2015; 386: 46–55
- Prof Julie Bernhardt, The Florey Institute of Neuroscience and Mental Health, Austin Campus, Heidelberg, VIC 3084, Australia
- Led by physiotherapists and nurses
- July 2006-Oct 2014 (*8 years*)

Introduction

- "*Early mobilization*" post-stroke encouraged by multiple expert / consensus guidelines
  - "*Early mobilization*" is **poorly defined**
  - **No strong scientific (or conflicting) evidence to date**
    - 3 prior studies including a total of 159 patients
- **AVERT** = largest trial
  - >10X size of combined early mobilization trials
- Impetus of study was to **prove** the benefit and **support** a long-held practice

Arguments

- *Rationale* for early mobilization
  1. Negate “harmful effects” of prolonged bed rest and immobility-related complications (bed sores, DVT, UTI, deconditioning)
  2. Possibly target a time-frame where “neuro-plasticity” could alter long-term outcomes for patients
- *Rationale* why early mobilization could be ***deleterious*** (<24h post CVA)
  1. Ischemic penumbra insufficiently perfused (gravity)
  2. Damaging HTN (induced by activity)
  3. More OOB (out of bed) = more at risk for falls
  4. *More risky*: post ICH and post IV-tPA
     - ? Inc. hemorrhage

Background

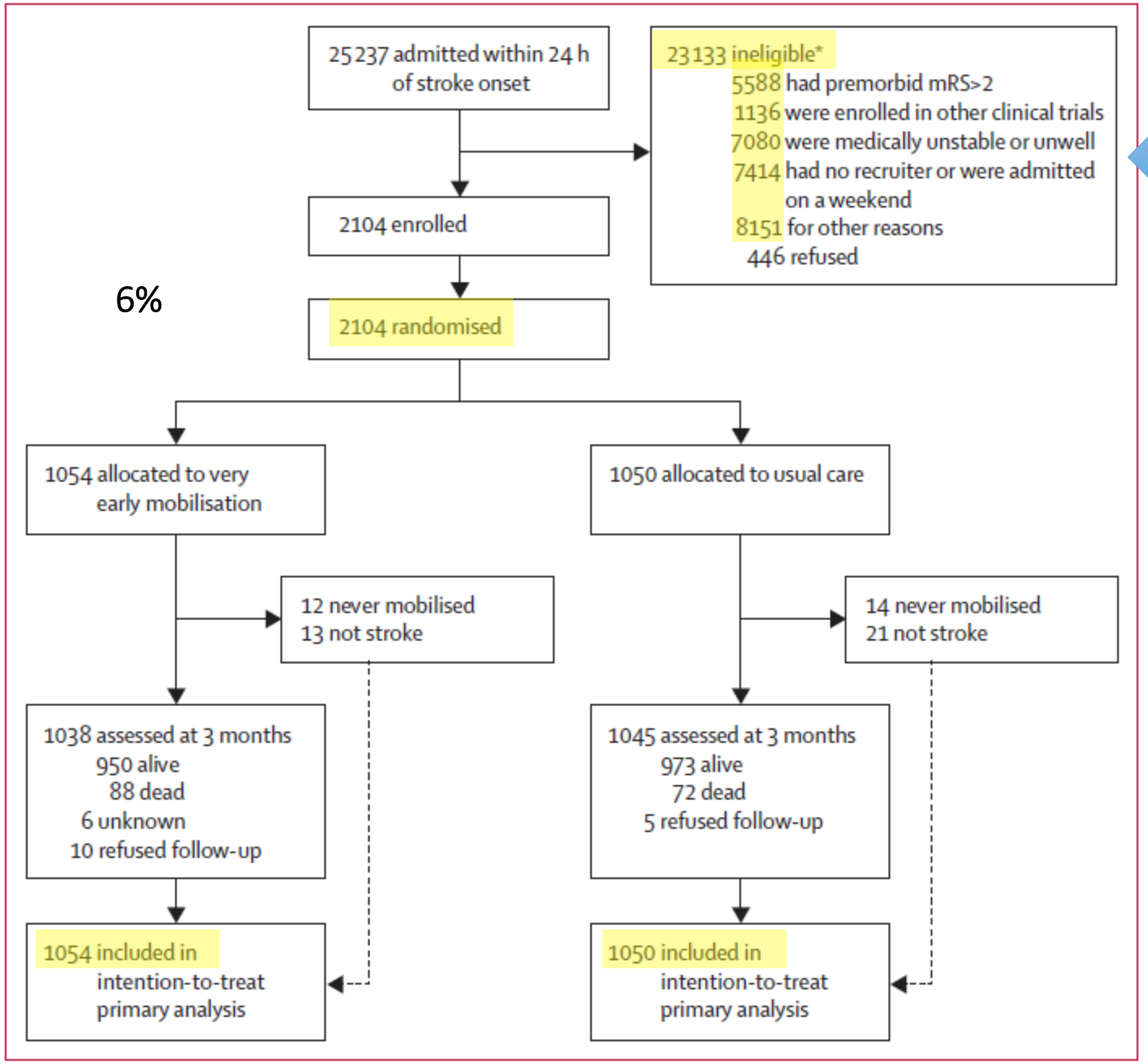
- Hypothesis
  - Very early OOB (<24h) with frequent sessions is superior to traditional mobilization (>24h) with less frequent and lesser intensity sessions
    - Increased QOL at 3 months, reduce complications, accelerate gait recovery with no increase in neurological complications
- Large and pragmatic design
  - Large and small stroke units
  - Urban and regional centers
  - Existing clinical staff as intervention team
  - All strokes “lumped” together
    - *Ischaemic (including all stroke mechanisms seemingly), ICH, post IV-Tpa….*

Methods

Parallel group, single-blind, international, RCT, 56 stroke units total, 5 countries

Rankin Modified Scale Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

- Exclusion
  - MRS >2 premorbid
  - No response to voice
  - SAH
  - Immediate
    - ICU admission
    - Surgery
    - “early deterioration”
    - Serious medical illness or unstable coronary condition
  - Vitals
    - SBP <100mmHg, >220mmHg
    - O2 sat <92% (with O2 supplement)
    - HR <40 or > 100 BPM
    - T > 38.5 C
  - Palliative admission



6%

Interesting to see who was excluded

Figure 1: Trial profile

Intervention

- “Usual care”
  - At discretion of site
- Very early mobilization group
  1. Begin <24h post CVA
  2. Focus in sitting, standing, walking (OOB activity)
  3. Result in at least 3 ***additional*** OOB sessions per day
- **End point** = 14d intervention or until D/C from stroke unit

Outcome measures

- Primary = Favourable (mRS 0-2) vs poor (mRS 3-6) @ 3 months

- Secondary =
  - Death
  - Ordinal shift of the mRS
  - Non-fatal serious adverse events at 3 month
  - Time taken to achieve unassisted walking >50 m
  - Proportion of patients achieving unassisted ambulation at 3 months

Results

Striking difference between this and prior mobilization studies

Daily OOB (sessions)
Daily OOB (time)
Until D/C or 14d post CVA

	Very early mobilisation (n=1054)	Usual care (n=1050)	p value	Median shift (95% CI)
Time to first mobilisation (h)	18·5 (12·8–22·3; n=1042*)	22·4 (16·5–29·3; n=1036*)	<0·0001	4·8 (4·1–5·7)
Frequency per person†	6·5 (4·0–9·5)	3 (2·0–4·5)	<0·0001	3 (3–3·5)
Daily amount per person (min)‡	31 (16·5–50·5)	10 (0–18)	<0·0001	21·0 (20–22·5)
Total amount per person (min)§	201·5 (108–340)	70 (32–130)	<0·0001	117 (107–128)

Data are median (IQR) or median (IQR; n), unless otherwise indicated. Dose data for very early mobilisation includes components of both usual care and very early mobilisation. Frequency is derived from nursing and therapist data. Amount (min) is derived from physiotherapist data only. Median estimates include days when time or number of out-of-bed sessions were zero—ie, the patient was recorded as not getting up on that day or for that session. *12 patients were missing from the very early mobilisation group and 14 patients were missing from the usual care group. Missing patients were never mobilised, either because of an early serious adverse event, decision to palliate, or early death or transfer from the stroke unit. For these patients, therapy and nurse recording forms were completed throughout their stroke-unit stay, with zero time and zero sessions. †Daily sessions of out-of-bed activity. ‡Min per day spent in out-of-bed activity. §Total amount is over the length of stay or until 14 days after stroke (whichever took place first).

***Table 2*: Intervention summary**

- *Distinct* well executed intervention
- They achieved what the study set out to do

@ 3 MONTHS

	Very early mobilisation (n=1038*)	Usual care (n=1045*)	Adjusted analysis		Unadjusted analysis	
			OR, generalised OR, or HR† (95% CI)	p value	OR generalised OR, or HR† (95% CI)	p value
Primary						
Favourable outcome‡	480 (46%)	525 (50%)	0·73 (0·59–0·90)	0·004	0·85 (0·72–1·0)	0·068
Secondary						
mRS category	..	..	0·94 (0·85–1·03)	0·193	0·94 (0·85–1·03)	0·202
0	90 (9%)	96 (9%)	..	..	..	..
1	200 (19%)	204 (19%)	..	..	..	..
2	190 (18%)	225 (22%)	..	..	..	..
3	238 (23%)	218 (21%)	..	..	..	..
4	140 (14%)	127 (12%)	..	..	..	..
5	92 (9%)	103 (10%)	..	..	..	..
6	88 (8%)	72 (7%)	..	..	..	..
Walking 50 m unassisted§	6 (5–7; n=1051)	7 (6–8; n=1049)	1·04 (0·94–1·15)	0·459	1·05 (0·95–1·16)	0·331

Data are n (%) or median (IQR; n), unless otherwise indicated. All analyses are adjusted for baseline National Institutes of Health Stroke Scale score and age. OR=odds ratio. HR=hazard ratio. mRS=modified Rankin Scale. *16 patients were missing from the very early mobilisation group and five patients were missing from the usual care group. These 21 patients declined follow-up or could not be found. Missing data were analysed according to our intention-to-treat strategy assuming missing at random. The appendix shows results of the sensitivity analysis. †Point estimates are ORs for the primary outcome, generalised ORs for the secondary outcome of mRS category, and HRs for the secondary outcome of walking unassisted. ‡mRS 0–2. §Time at which 50% of participants walked. The number walking unassisted includes all patients who were recorded as having walked 50 m unassisted in the first 3 months. This number might include patients for whom we were unable to obtain 3 month mRS.

***Table 3*: Outcomes at 3 months**

Shift Analysis

Dichotomized Outcome

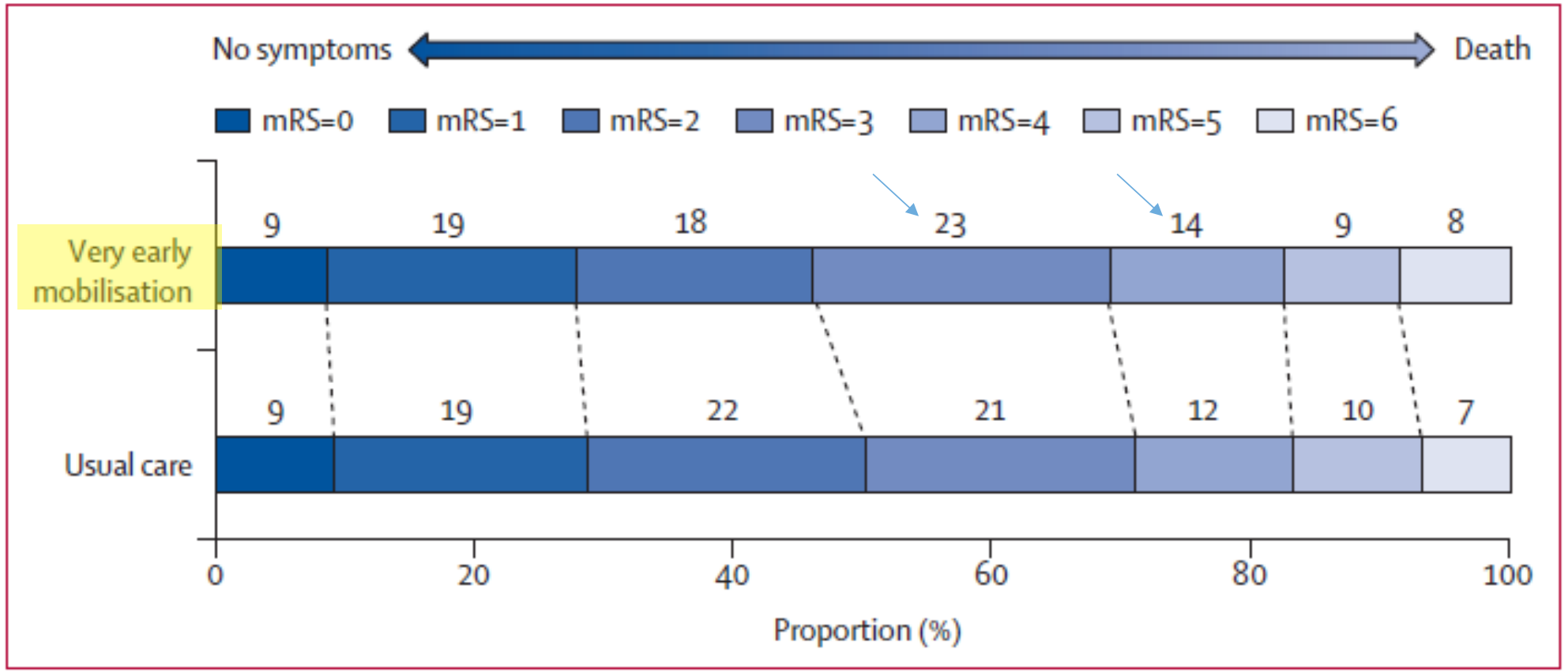


Figure 2: Patients achieving each mRS score at 3 months
mRS=modified Rankin Scale.

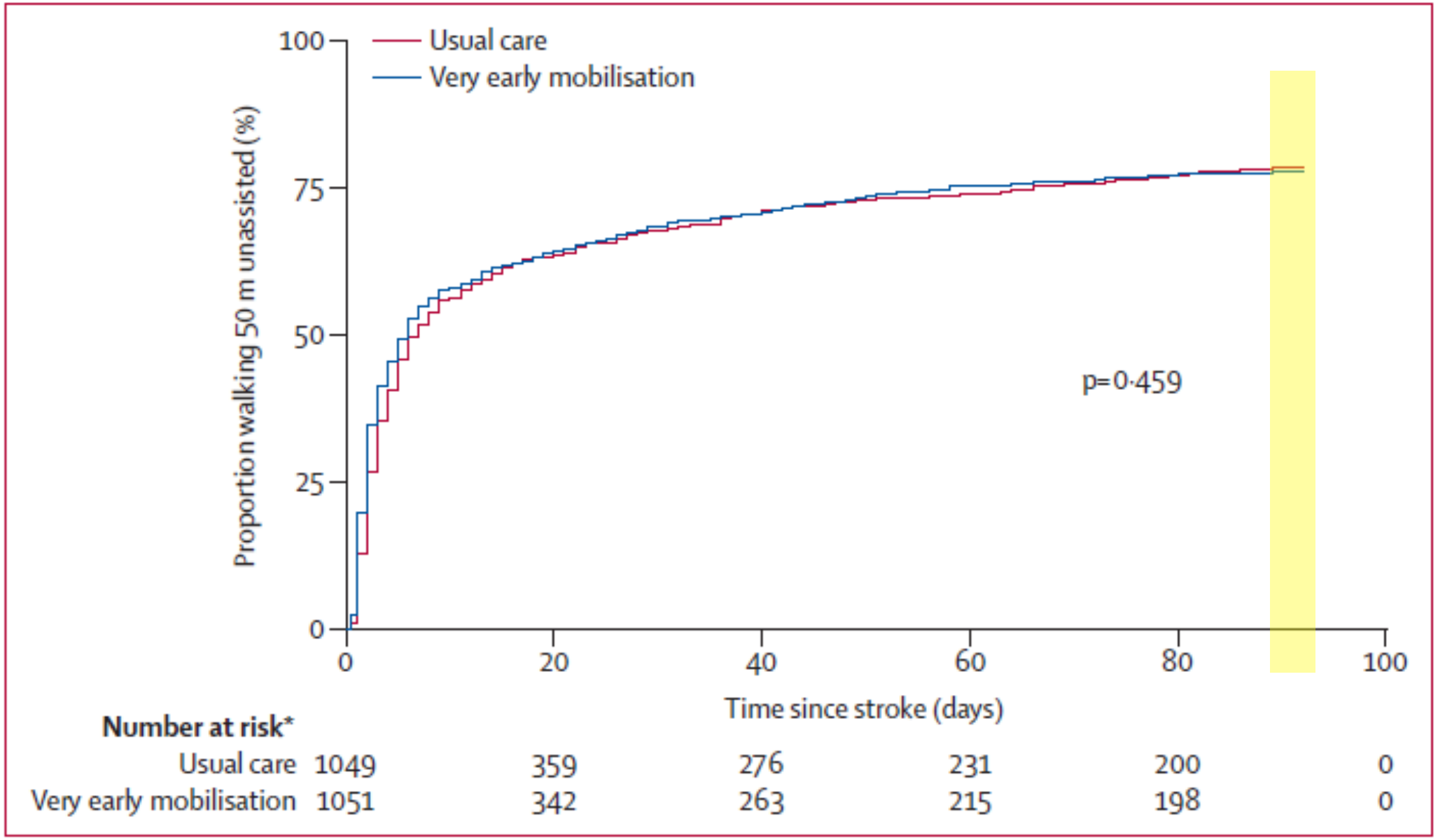


Figure 3: Time to walking unassisted 50 m by 3 months

*Number of patients who had not achieved walking.

Death and Serious Complications at 3 months

- *Very early mobilization* *vs. Usual care*

- Death 88/1048 (8%) ***vs*** 72/1050 (7%) OR 1.34 (0.93-1.93) p 0.113 **NS**

- Non-fatal serious adverse events
  - OR 0.88 (0.72-1.07) p 0.194 **NS**
- Immobility related AEs i.e, PE, DVT, UTI, pressure sores, pneumonia
  - OR 0.92 (0.62-1.35) p 0.665 **NS**
- Neurological AEs i.e, stroke progression or recurrent CVA
  - OR 1.26 (0.95-1.66) p 0.108 **NS**

Subgroup Analyses

- All favoured “usual care”
- “Signal” from pre-specified subgroup for **reduced** odds of favourable outcome
  - Severe CVAs
  - ICH
- IV-rTPA – No evidence for harm in early subgroup

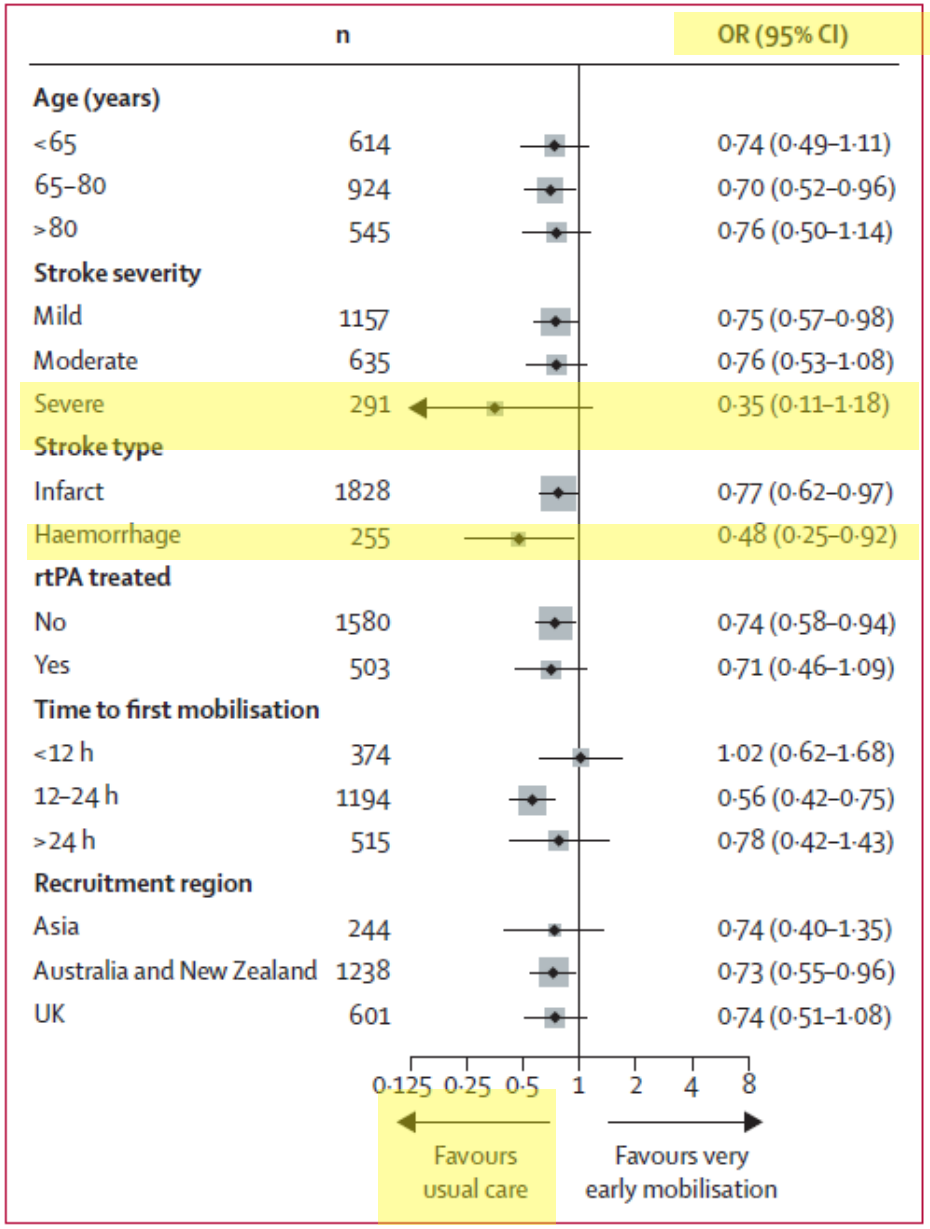


Figure 4: **Prespecified subgroup analyses**
None of the individual subgroup analyses had significant treatment-by-subgroup interactions (all p>0·05). OR=odds ratio. rtPA=recombinant tissue plasminogen activator.

Strengths

- « **Mega-trial** »; very large numbers of participants
  - For difficult to ever reproduce
  - Largest for acute stroke rehab *ever* done
- Real life application as multi-country (5), long-term reporting « **Pragmatic** »
  - « Generalizeable », good external validity
- Simple intervention; potentially **large** impact
- Inexpensive
- Exluded medically ill patient's and titrated exercise to BP initially
- **<1%** of patients missing from primary endpoint calculation –data set is **robust**
- Same **rigorous standards** as drug or device trials

Limitations

- Unexpected and controversial outcome
- *"Routine" post-stroke care changed in 8 years*
  - Over course of trial 60% "usual care" started OOB sessions <24h of stroke onset.
  - Likely explains for lack of difference in the "immobility" related complications b/w groups
    - Would **<12 h** have changed outcome
- Unclear why they "*lumped*" all strokes together in the primary outcome analysis (probably to enhance external validity)
  - Not reality of stroke practice
  - Primary outcome measure (*dichotomized to mRS*) not sensitive enough
- Will be impossible to ***disprove*** the demonstrated effect; hard to replicate a study of such magnitude in the future

Questions

- Merci

Future: Should this study change our practice?

- This trial will (partly) influence our practice
  - Early ***and*** more is *not* always better in the acutely injured brain (from CVA); especially in ICH and “severe” strokes.
  - Future rehab trials?
    - Dose-response on efficacy and safety outcomes
    - PROM and device mobilizations
    - Basic pathophysiology of post-CVA rehab
    - Analyze groups based on pathophysiology of the CVA