Unassisted breathing and death as competing events in critical care trials

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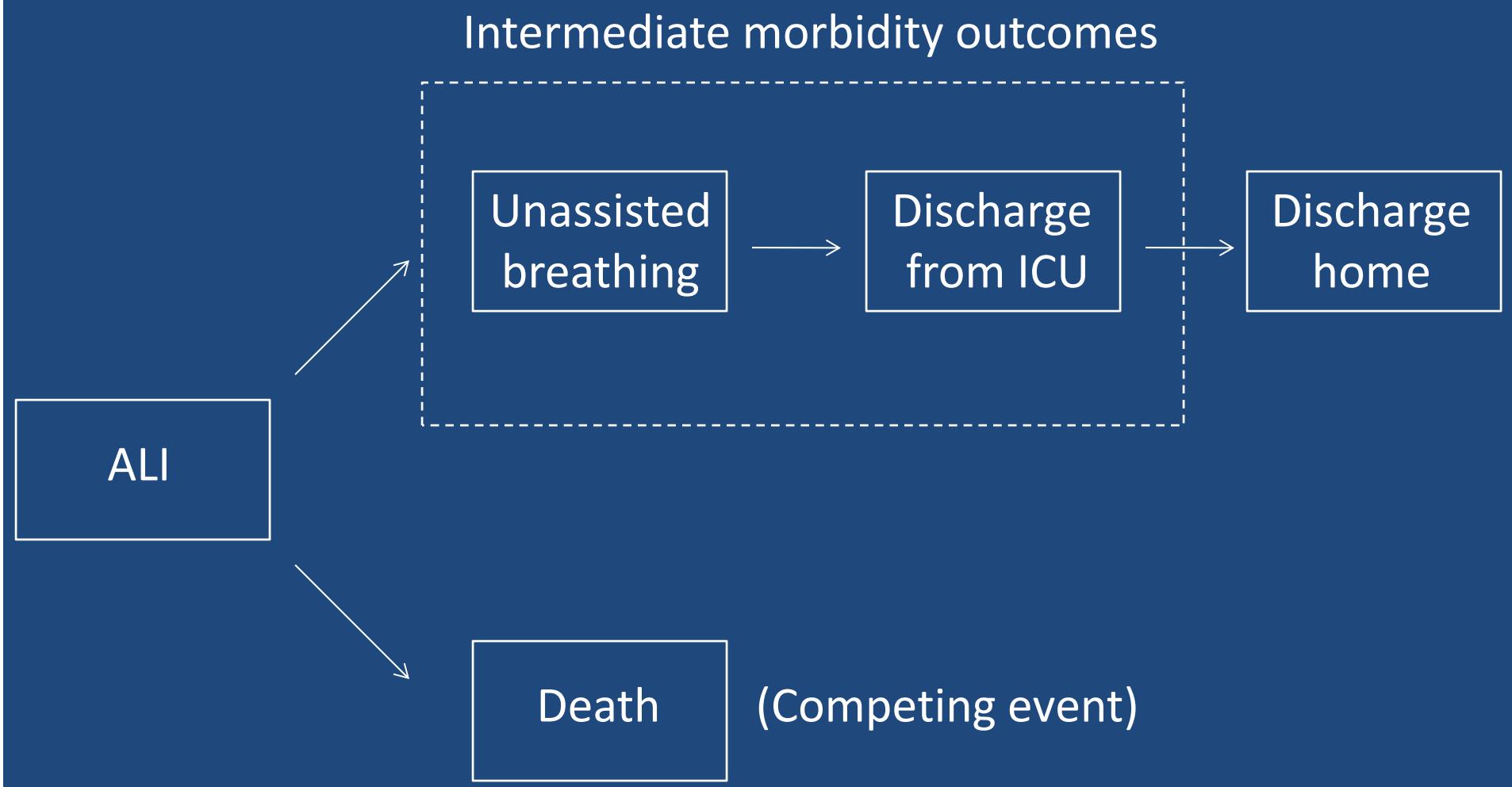
Objectives

- Jointly model the frequency and timing of unassisted breathing and death in critical care trials.
- Characterize differences in the frequency, timing or both of these two clinical events between study groups.

Clinical outcomes in acute lung injury



Ventilator-free days score (VFDS)

- Most common definition (at 28 days):
  - VFDS = 0: death $\leq$ 28 days.
  - VFDS = (28 - x): number of days without mechanical ventilation in the first 28 days.
  - VFDS = 0: Mechanical ventilation > 28 days.

“Turn a knob, save a life”

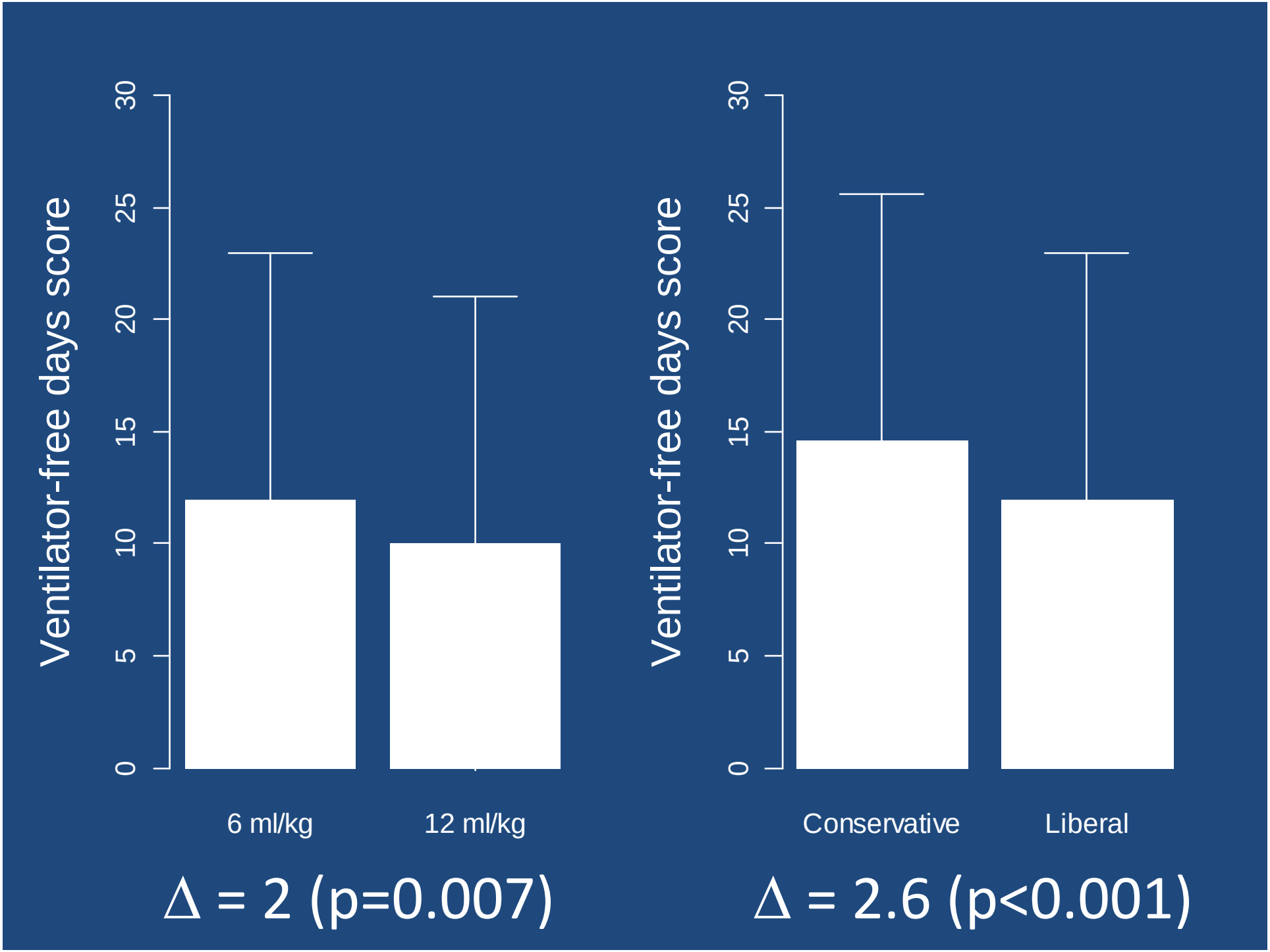
- Ventilation with “traditional” tidal volumes (10-15 ml/kg) may cause stretch-induced injury.
- Does ventilation with lower tidal volumes improve clinical outcomes in patients with ALI?
- Mortality was lower for 6 ml/kg vs 12 ml/kg (31% vs 40%; p = 0.007).
- VFDS were greater for 6 ml/kg vs 12 ml/kg (mean 12 vs 10; p = 0.007).

ARDS Network. N Engl J Med 2000;342:1301–1308

“Dry lungs are happy lungs”

- Fluid restriction may improve lung function but jeopardize extrapulmonary organ perfusion.
- Does fluid management with lower vs higher intravascular pressure improve outcomes?
- 60-day mortality was 26% in the conservative arm vs 28% in the liberal arm ($p = 0.30$).
- VFDS were greater in the conservative arm vs liberal arm (mean 14.6 vs 12.1; $p < 0.001$).

ARDS Network. N Engl J Med 2006;354:2564–2575

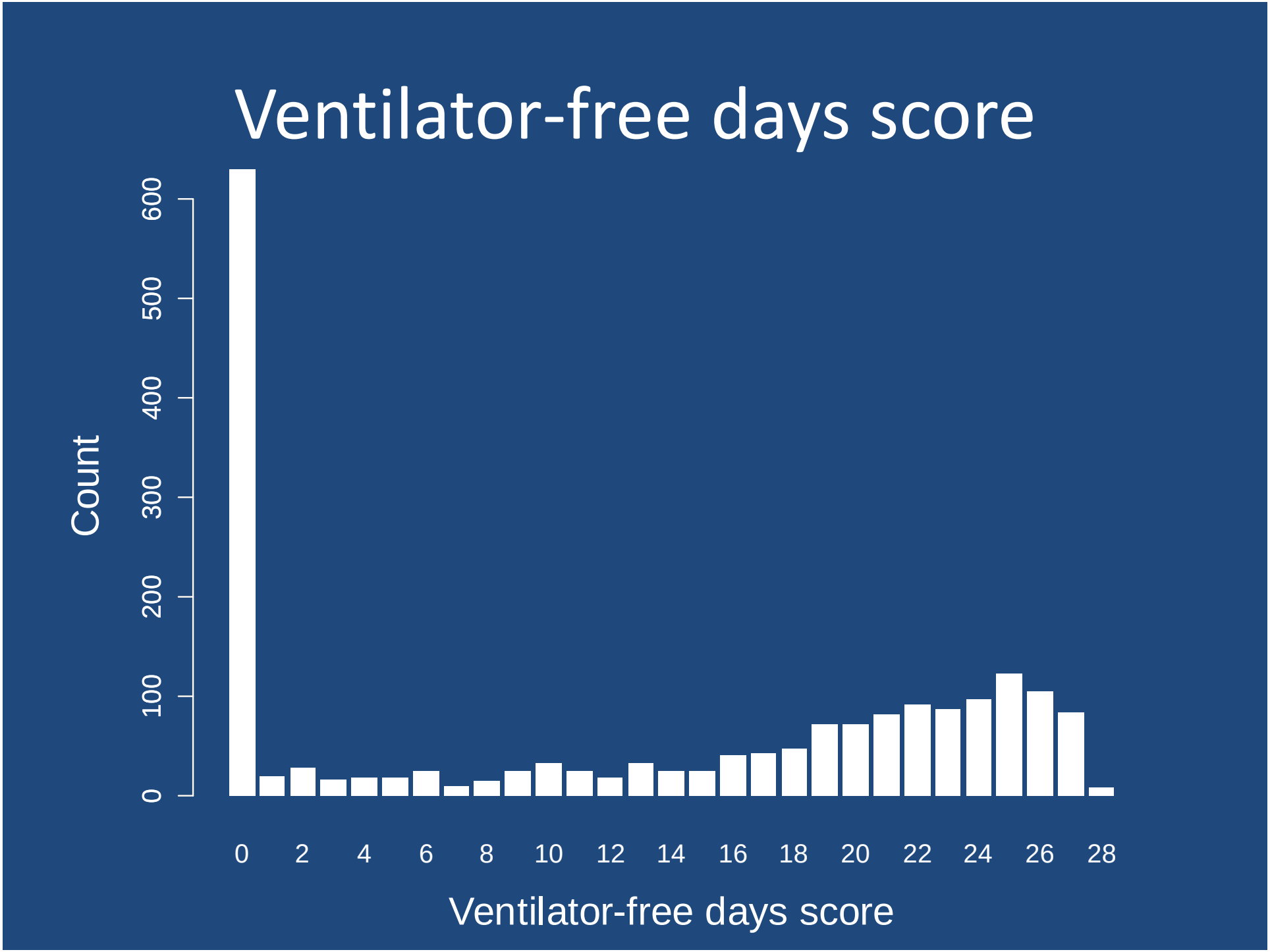

Ventilator-free days score
0
5
10
15
20
25
30
6 ml/kg
12 ml/kg
Δ = 2 (p=0.007)
Ventilator-free days score
0
5
10
15
20
25
30
Conservative
Liberal
Δ = 2.6 (p<0.001)

What does the VFDS measure?

- Similar differences in VFDS between study groups in both trials.
- How to interpret the difference in VFDS for each trial?
- What does a difference of “2” VFDS mean?

Problems with the VFDS

- Strongly “abnormal” distribution.
- Cannot be modeled with any parametric probability distributions.
- Relies on non-parametric methods or central-limit theorem approximations for analysis.


Ventilator-free days score
Count
0
100
200
300
400
500
600
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
Ventilator-free days score

Problems with the VFDS

- A difference in VFDS may be due to a lower mortality and/or more days free of ventilation.
- The word “days” is confusing: cannot be used to interpret differences in VFDS.

Survival analysis for multiple events

- Standard methods in survival analysis can only accommodate one type of clinical event.
- Subjects without the event are censored at time of last follow-up.
- Non-informative censoring = censored subjects develop the event at the same rate if followed longer. Untenable for critical care outcomes.

Survival analysis for multiple events

- Censoring at time of death when unassisted breathing is the event of interest:
  - Violates assumption of survival analysis.
  - Doesn't describe realities of critical care outcomes.
  - Limited view of complexities of competing events.

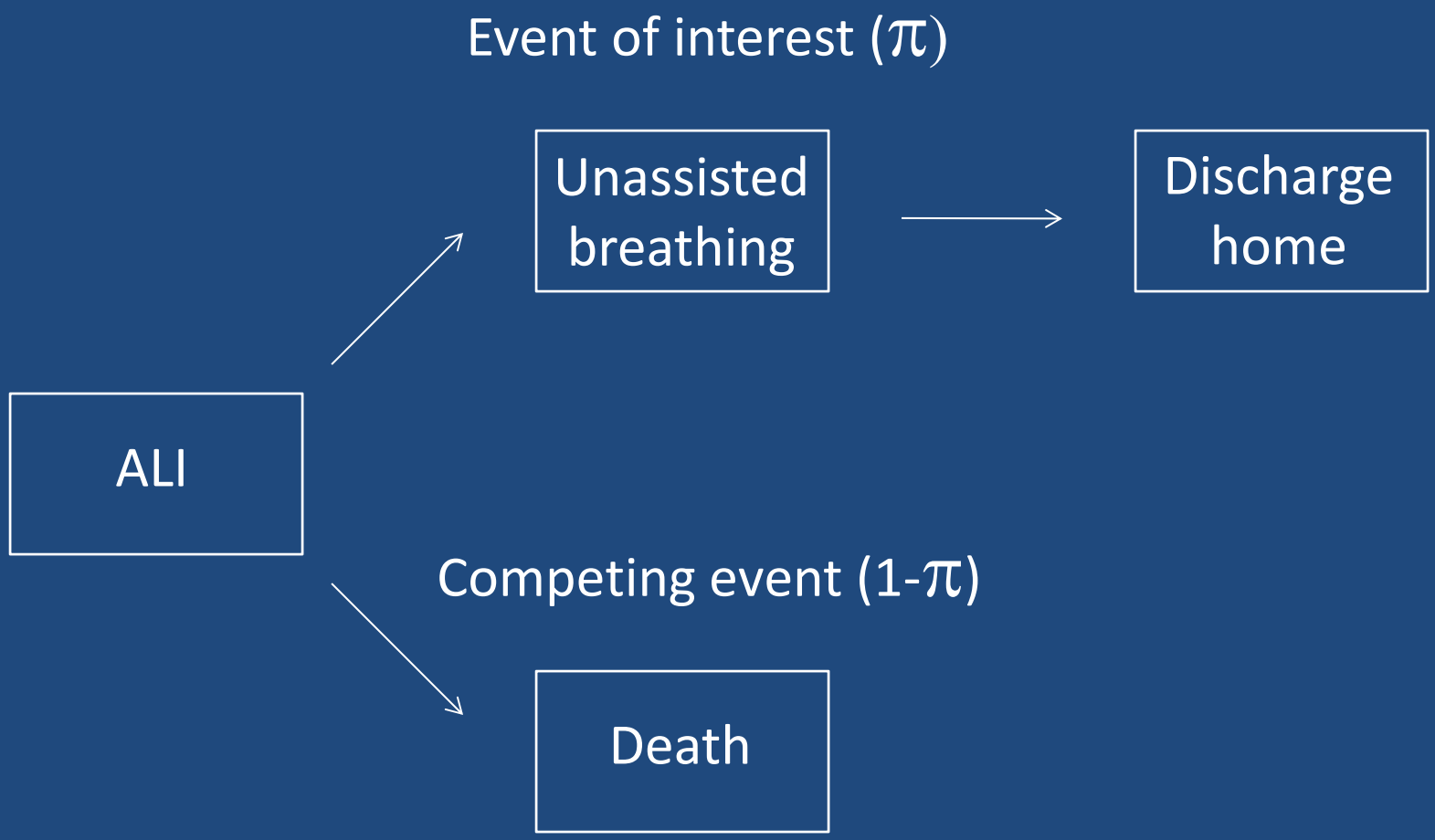
Competing risks

- Modeling strategy that allows multiple, competing events for time-to-event data.
- Competing events:
  - Hinder the observation of the primary event.
  - Alter the probability of occurrence of the primary event.

Competing risks

- Well-implemented statistical methods for "classical" competing risks.
- These methods assume that the rate of events between two groups is proportional over time.
- Therefore, cannot characterize differences in the "timing" of events (sustained, early, late, none?).

Competing events of UAB vs death



Checkley et al. Epidemiology 2010;21: 557–565.

Mixture models

- The mixture means a combination of probability distributions.
- In our application, the mixture model consists of:
  - A mixture probability (summary of the frequency of each competing event)
  - Parametric survival distribution (summary of the times of each competing event).

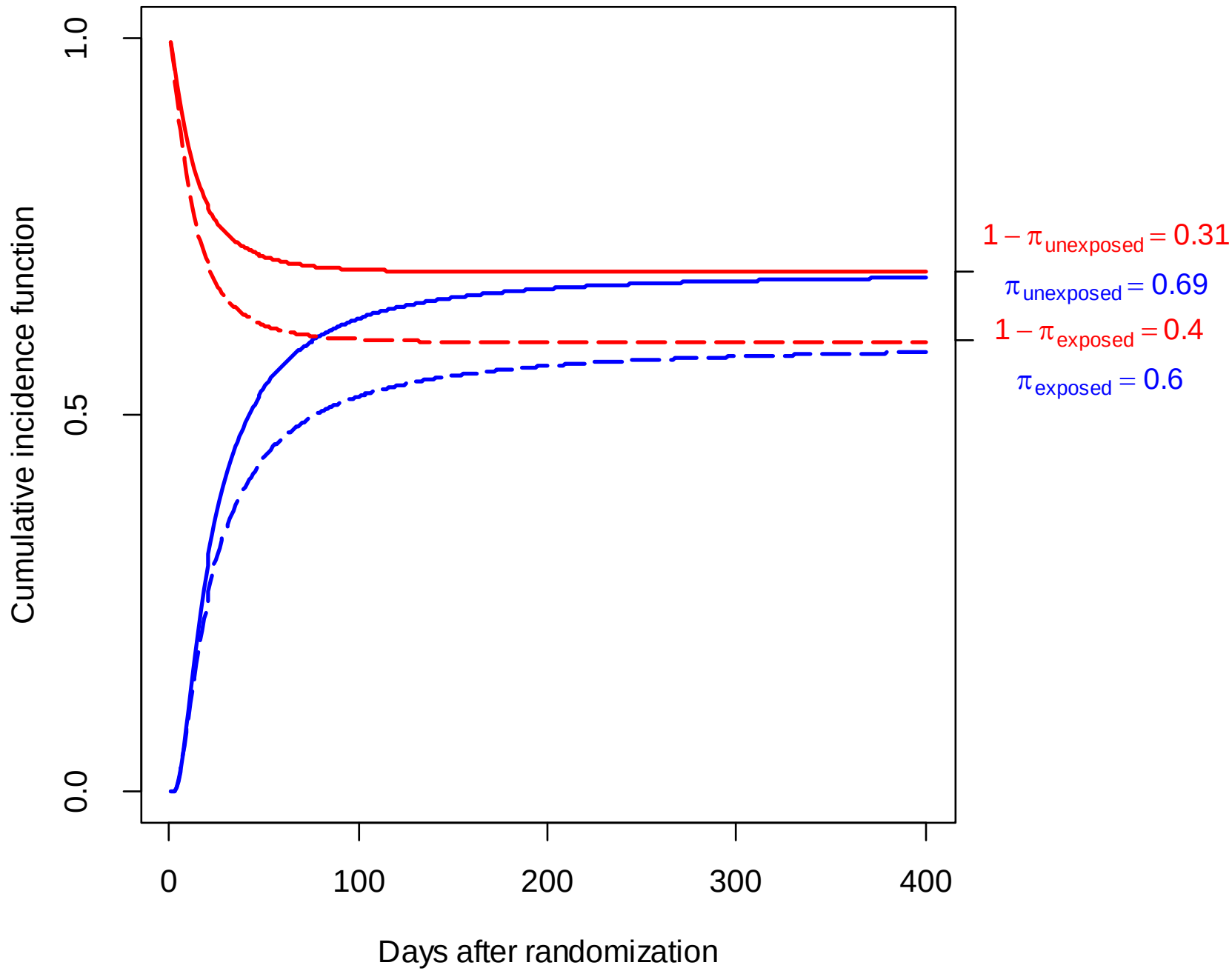
Generalized gamma distribution

- 3 parameters: location (β), scale (σ) and shape (λ).
- Probability density function:

$$f_{GG}(t) = \frac{|\lambda|}{\sigma t \Gamma(\lambda^{-2})} \left[\lambda^{-2}(e^{-\beta}t)^{\lambda/\sigma}\right]\exp\left[-\lambda^{-2}(e^{-\beta}t)^{\lambda/\sigma}\right]$$

Cumulative incidence function (CIF)

- Cumulative percentage of subjects who develop an event over a specified time period.
- For 1 event, CIF = 1 – Kaplan-Meier.
- For competing events:
  - CIF ≠ 1 – Kaplan Meier (subdistribution CIF).
  - Asymptote is the overall frequency for that event.


Cumulative incidence function
1.0
0.5
0.0
0
100
200
300
400
Days after randomization
$1 - \pi_{unexposed} = 0.31$
$\pi_{unexposed} = 0.69$
$1 - \pi_{exposed} = 0.4$
$\pi_{exposed} = 0.6$

Ratio of cumulative incidences (RCI)

- Relative change in the cumulative percentage of subjects who achieve UAB by day “t”.
- At any given time, the RCI of UAB of A to B:
  - Favors A if RCI > 1
  - Favors B if RCI < 1
- Asymptote of the RCI of UAB is the relative risk.

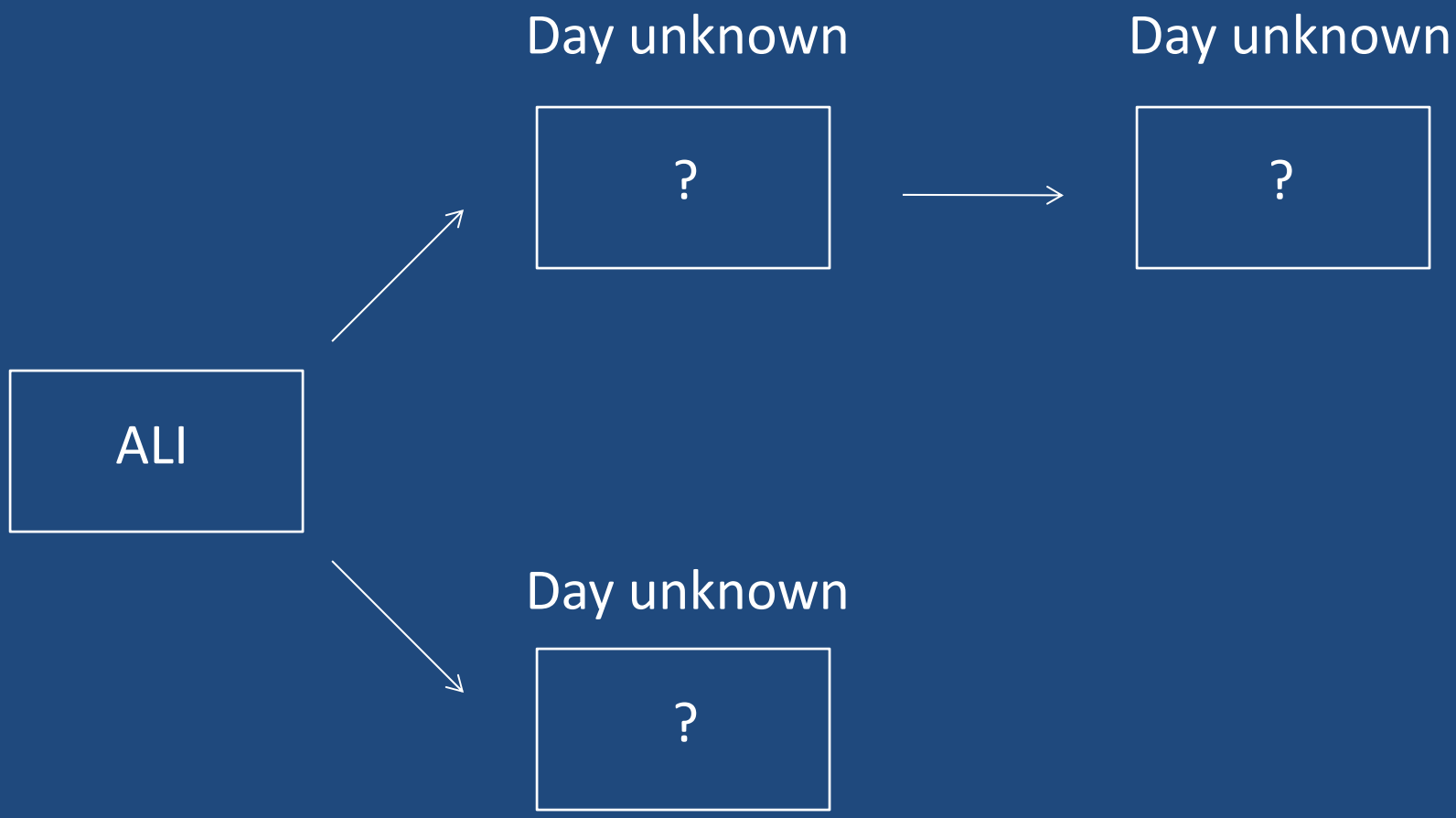
RCI of UAB: interpretation

- On day 5, the RCI of UAB of treatment A to B was 1.20 (95% CI 1.05 – 1.45).
- The percentage of ventilated patients who achieved UAB in treatment A on day 5 was 20% greater than that in treatment B.

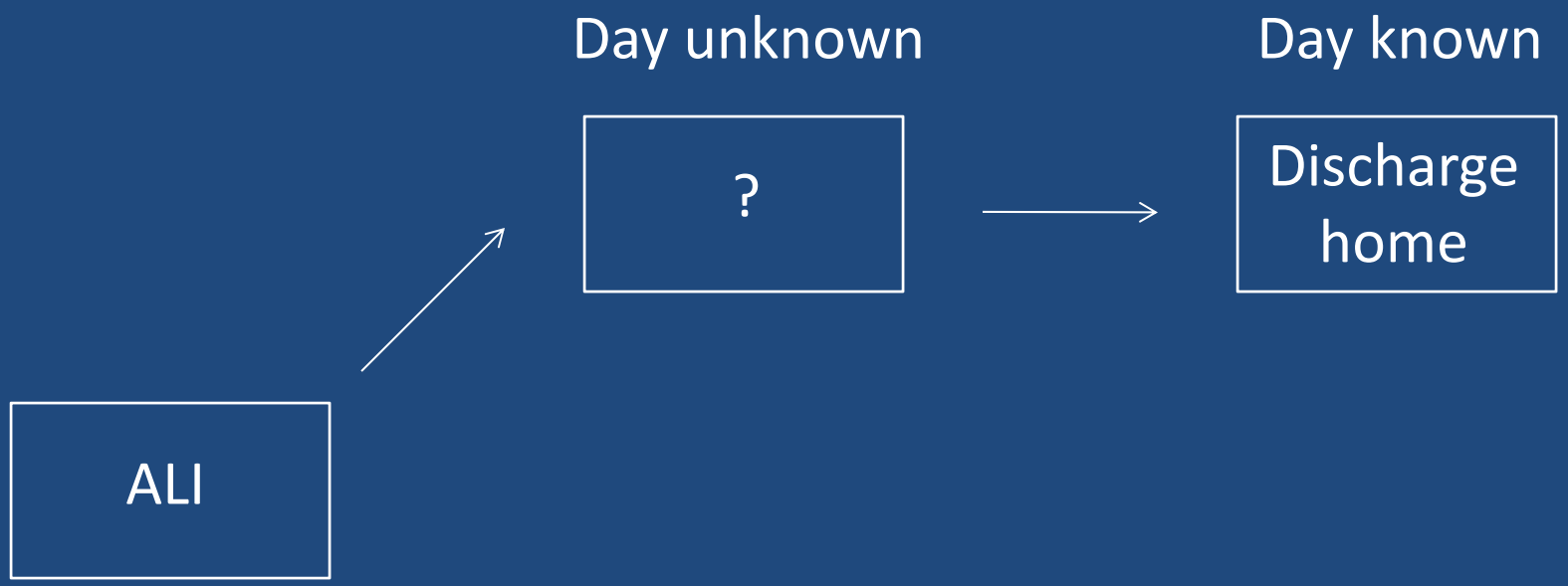
Types of censoring

- Right-censoring for UAB or death = participant did not achieve UAB (or discharge) nor death.
- Interval-censoring for UAB = exact day of UAB unknown but occurred between day 28 and day of discharge alive with UAB.

Right-censoring



Interval-censoring



Mixture model for competing risks

- Two generalized gamma distributions to model the times-to-UAB and times-to-death.
- The mixing probabilities are the overall frequencies of UAB (π) and death ($1 - \pi$).

$$\pi f(t) + (1 - \pi)g(t)$$

$$f(t) \sim f_{GG}(t; \beta_f, \sigma_f, \lambda_f)$$

$$g(t) \sim f_{GG}(t; \beta_g, \sigma_g, \lambda_g)$$

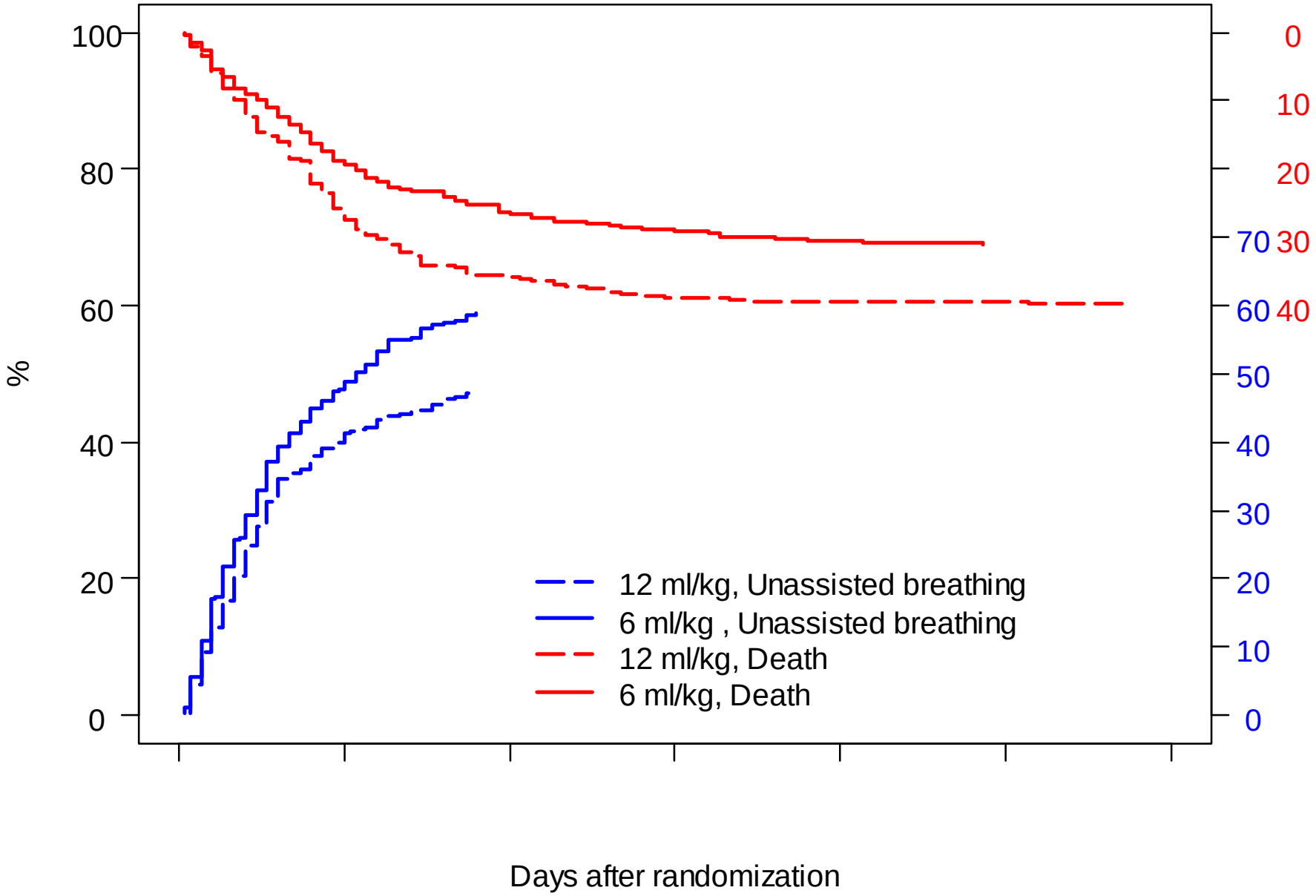
Mixture model for competing risks

- f(t) = density function for times-to-UAB.
- F(t) = survival function for times-to-UAB.
- CIF of UAB = $\pi[1 - F(t)]$
- RCI of UAB = $\dfrac{\pi_1 [1 - F_1(t)]}{\pi_0 [1 - F_0(t)]}$

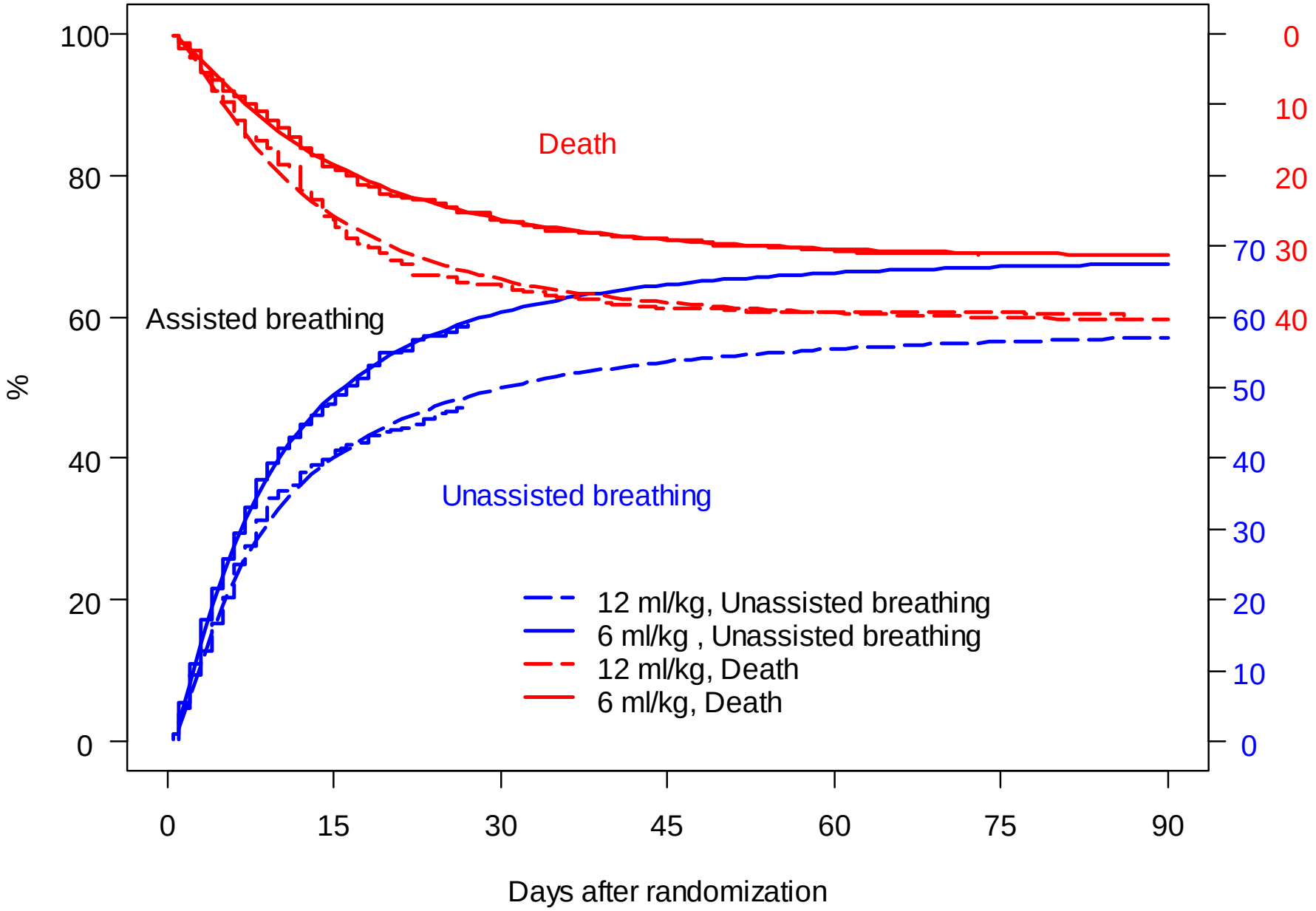
Statistical inference

- Maximum likelihood estimation of 14 parameters.
  - 7 parameters for each study group:
  - 3 for times-to-UAB (β_f, σ_f, λ_f), 3 for times-to-death (β_g, σ_g, λ_g), and 1 for the mixing probability (π).
- 1,000 bootstrap replicates to obtain 95% CI.

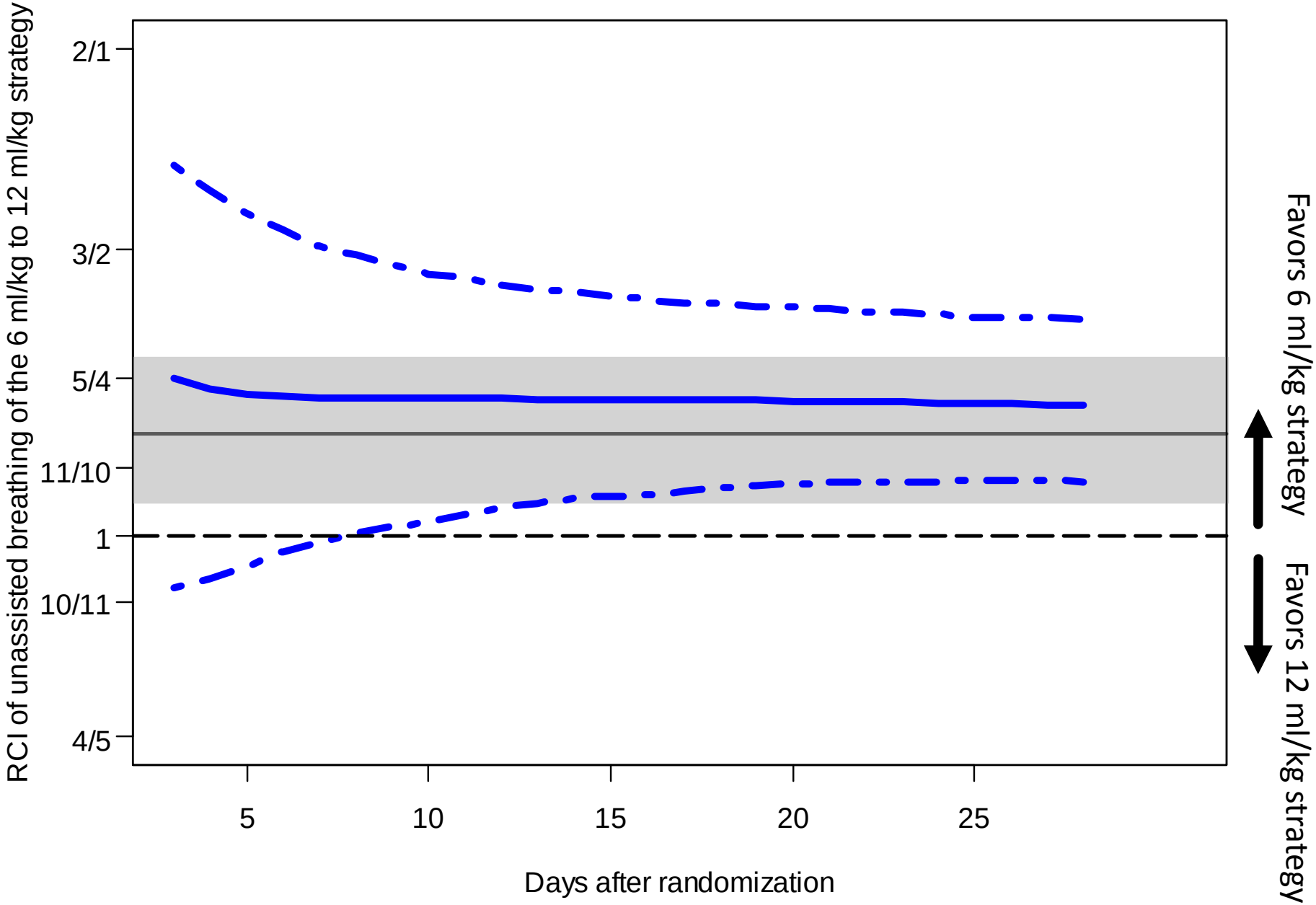
Tidal volume trial



Tidal volume trial



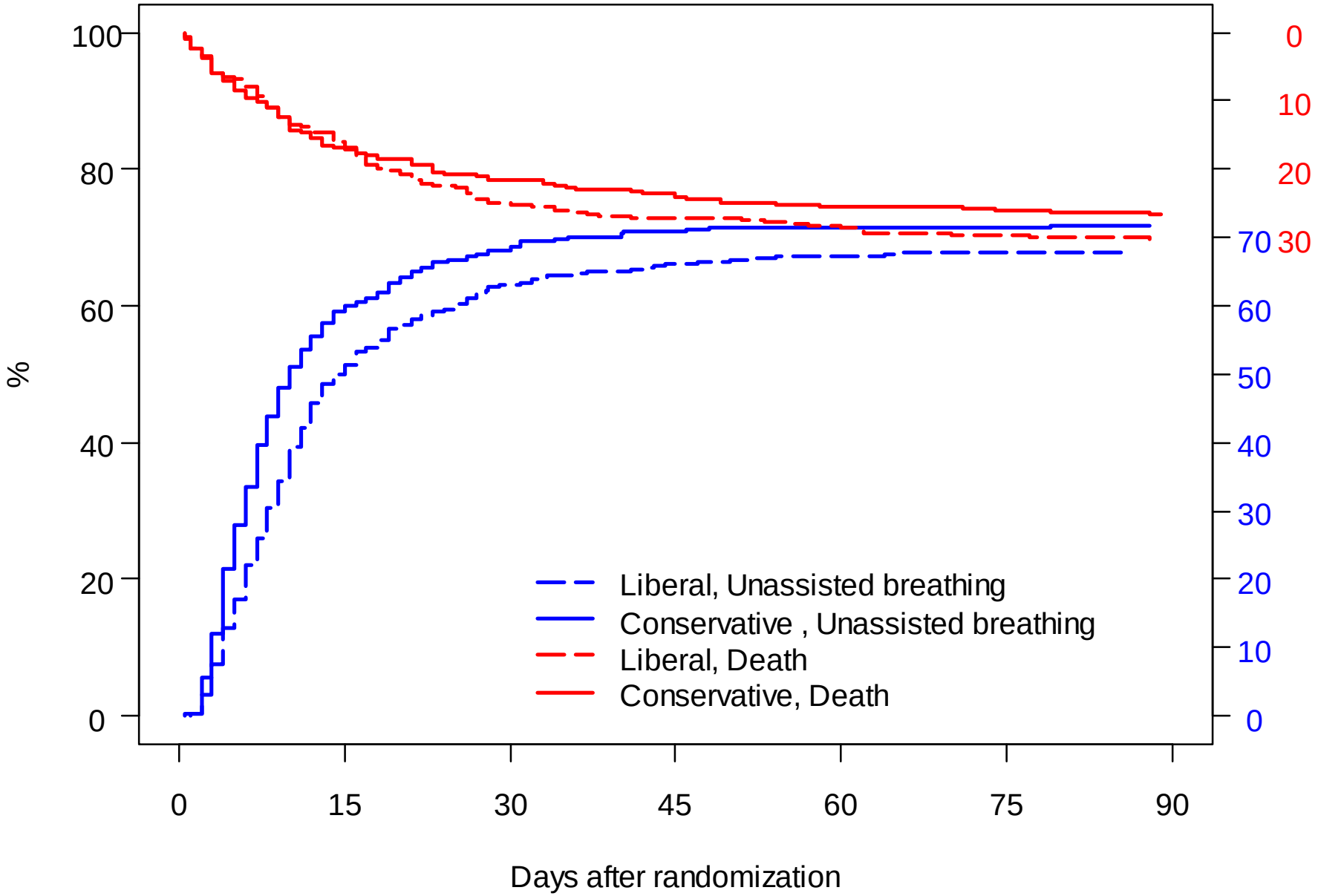
Tidal volume trial



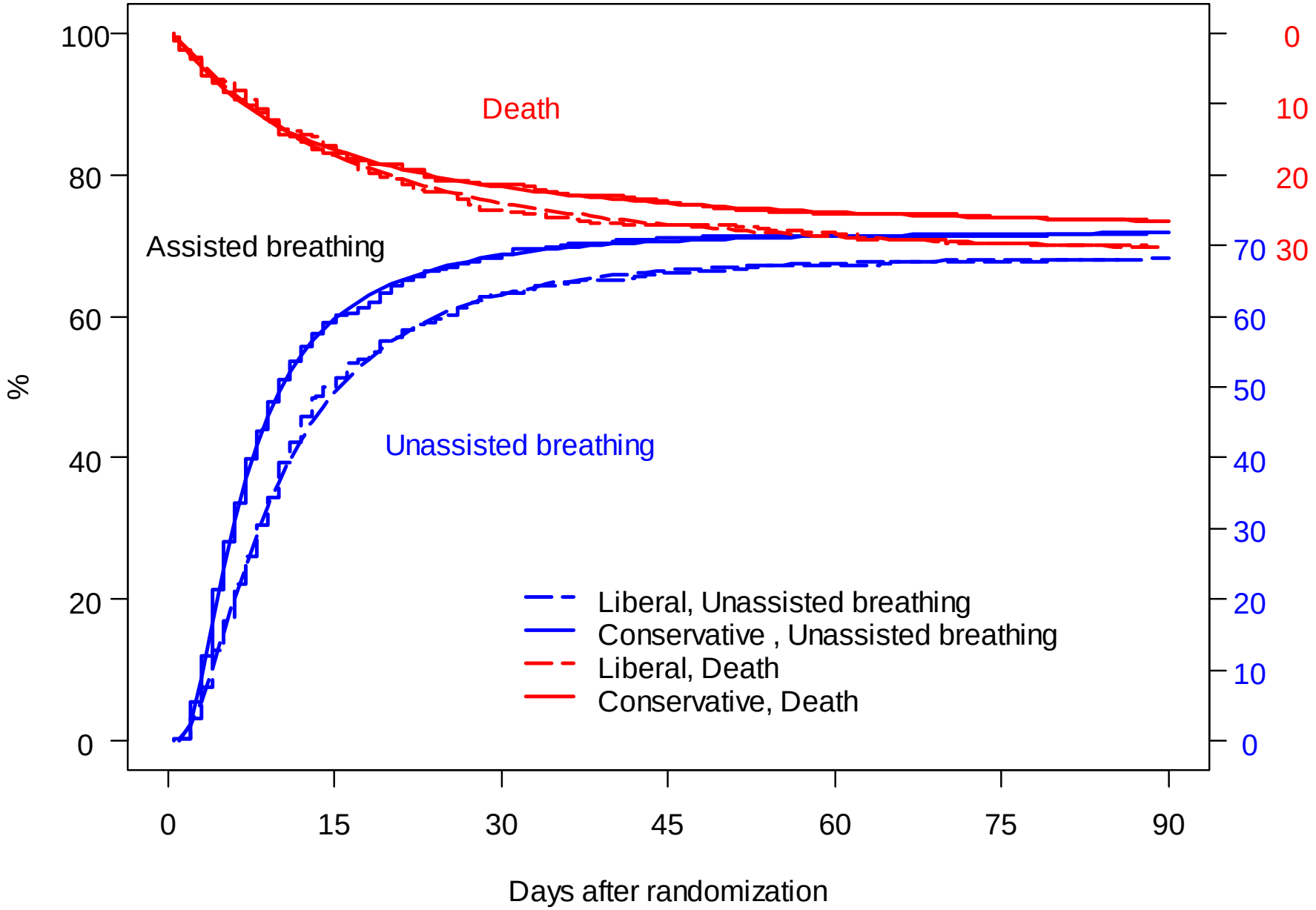
Results: tidal volume trial

- On average, the cumulative incidence of UAB was 20% greater for 6 ml/kg than for 12 ml/kg.
- RCI of UAB was not different from the overall RR of UAB (p=0.477).
- Differences in times-to-UAB between treatments was small.

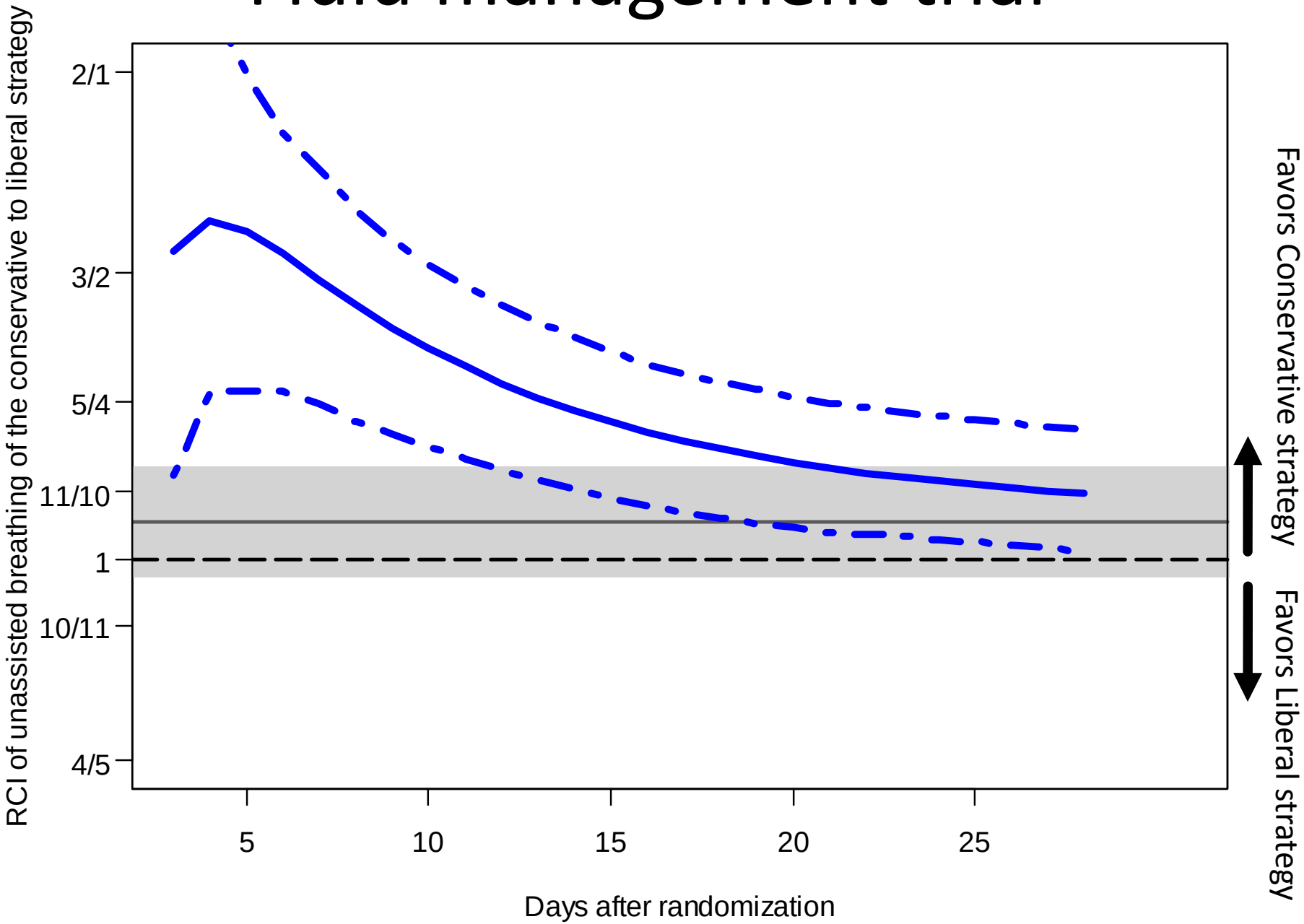
Fluid management trial



Fluid management trial



Fluid management trial



Results: fluid management trial

- Shortly after randomization, cumulative incidence of UAB was 50% greater in the conservative strategy.
- RCI of UAB was statistically greater than RR of UAB in the first 12 days ($p<0.001$).
- Patients in the conservative strategy achieved UAB earlier than patients in the liberal strategy.

Overall results

- Difference of “2” VFDS was different in both trials.
- Tidal volume trial: VFDS difference was due to a difference in mortality and not due to UAB.
- Fluid management trial: VFDS difference was due to earlier UAB and not due to mortality.

Advantages of our mixture model

- Fully parametric
- Standard methods to estimate parameters
- Easily accommodates R/L/interval censoring
- Covariates in the form of a regression

Advantages of our mixture model

- Free from proportionality of hazards.
- Complete description of the hazard function.
- We can calculate relative times.
- We can decompose the frequency and timing of events and interpret them separately.

Acknowledgements

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