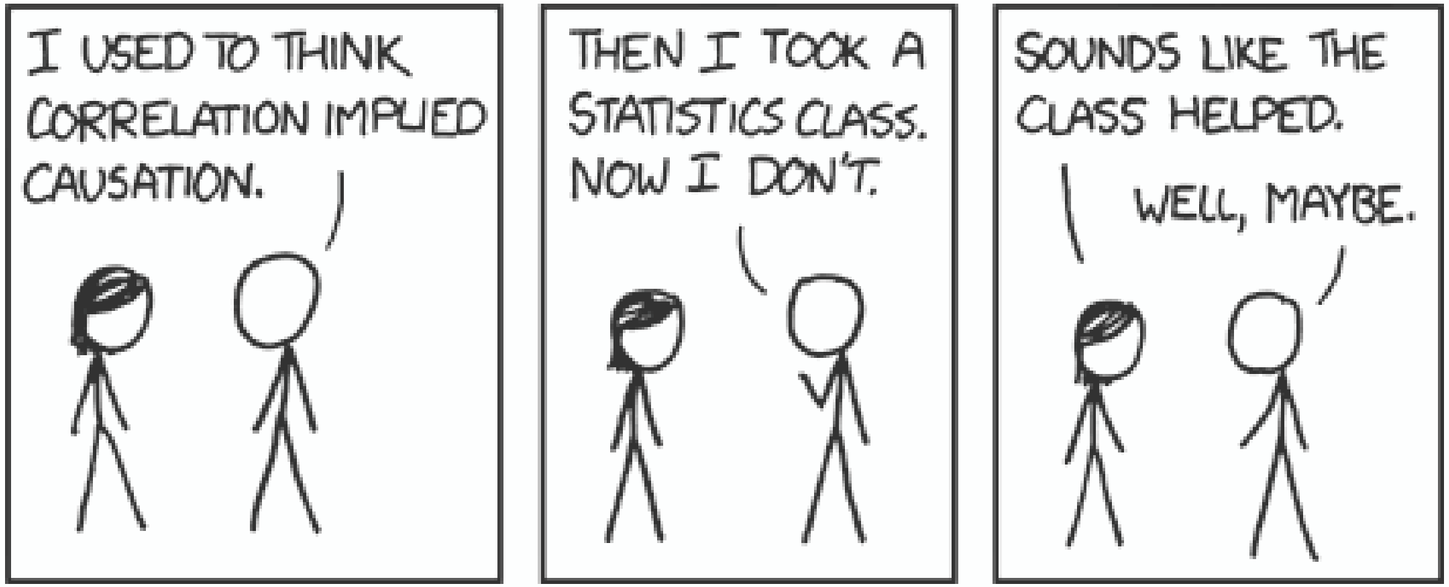
EMULATED TARGET TRIALS

EFFECTIVENESS OF LOW VOLUME AND LOW PRESSURE IN SEVERE HYPOXEMIC PATIENTS

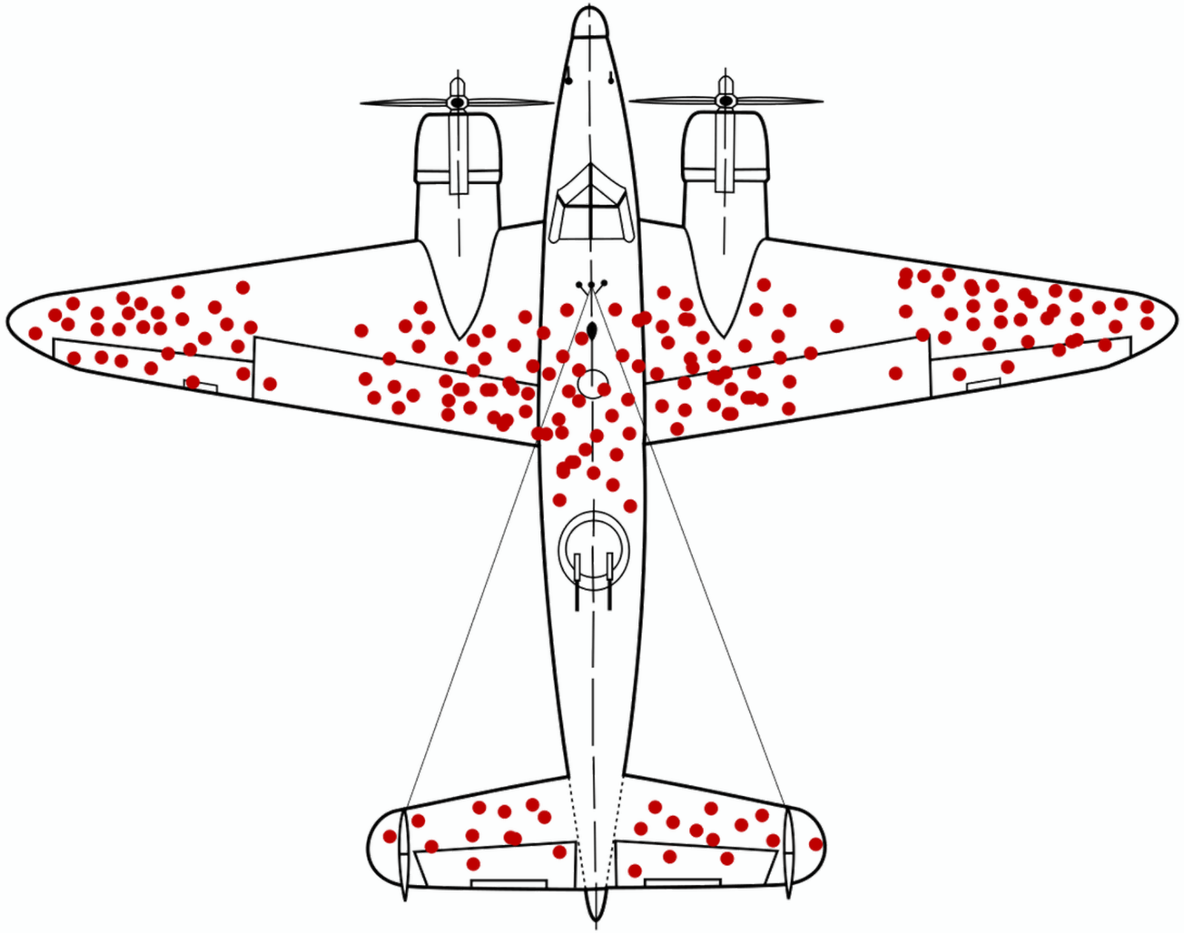
STEFANO FINAZZI
DEMETRIO MAGATTI
MARCO RANIERI

33° Meeting GiViTI
Pesaro 14 Novembre 2024

EFFICACIA TRATTAMENTO



BIAS



COMPLICANZE E MORTALITÀ

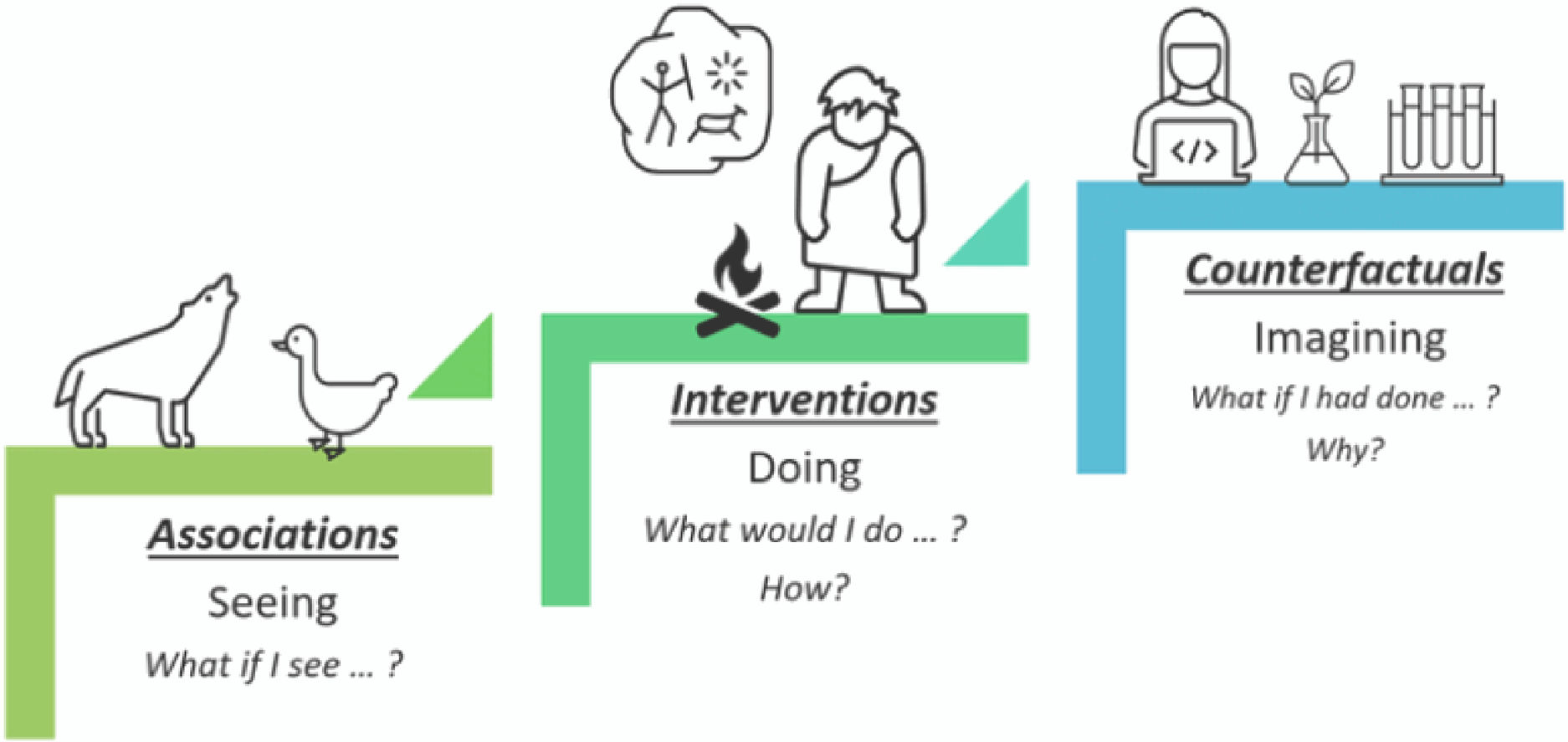
34% **Mortalità trauma cranico**

18% Con complicanze infettive

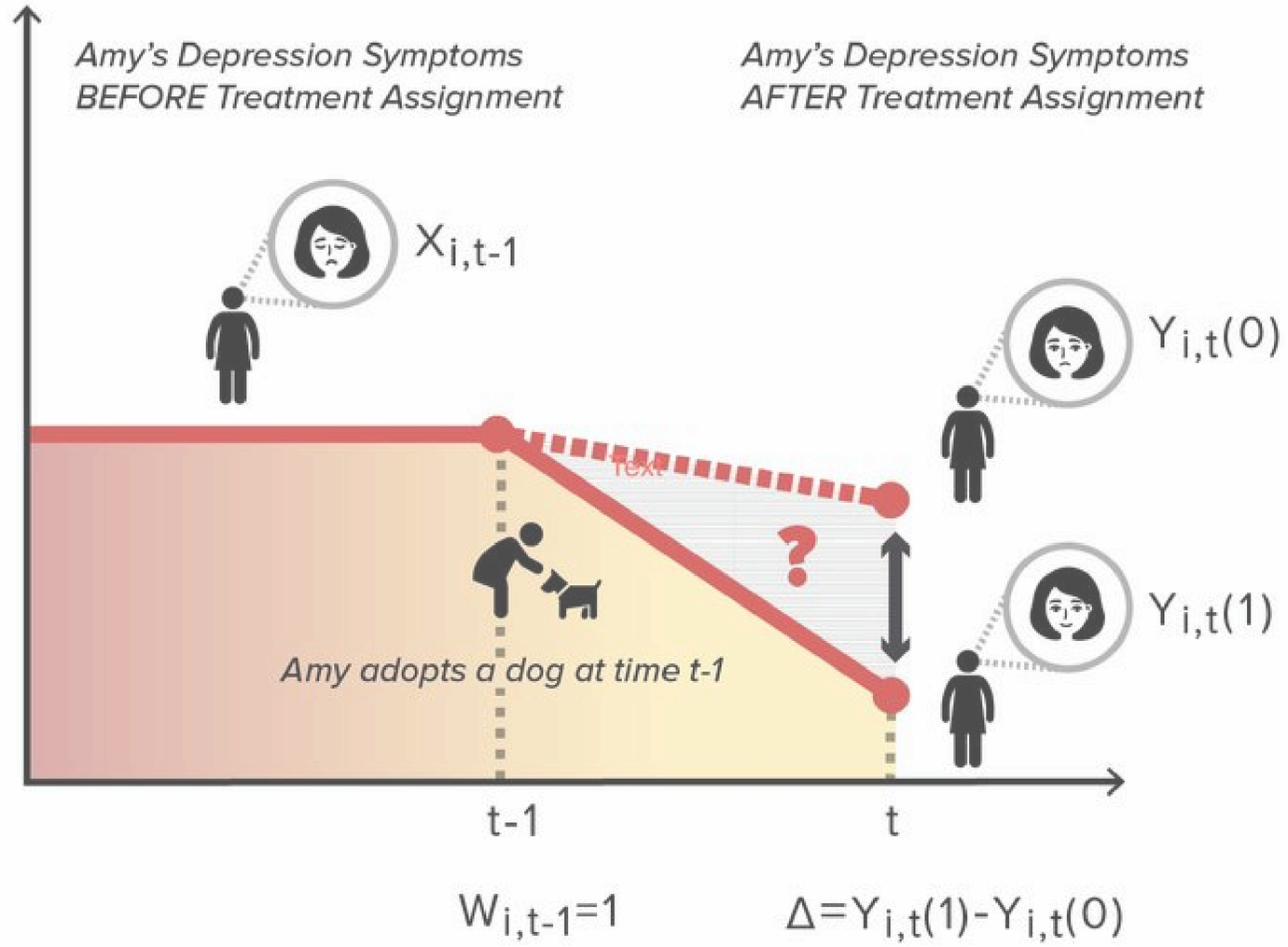
43% Senza complicanze

EFFICACIA TRATTAMENTO

WHAT IF?

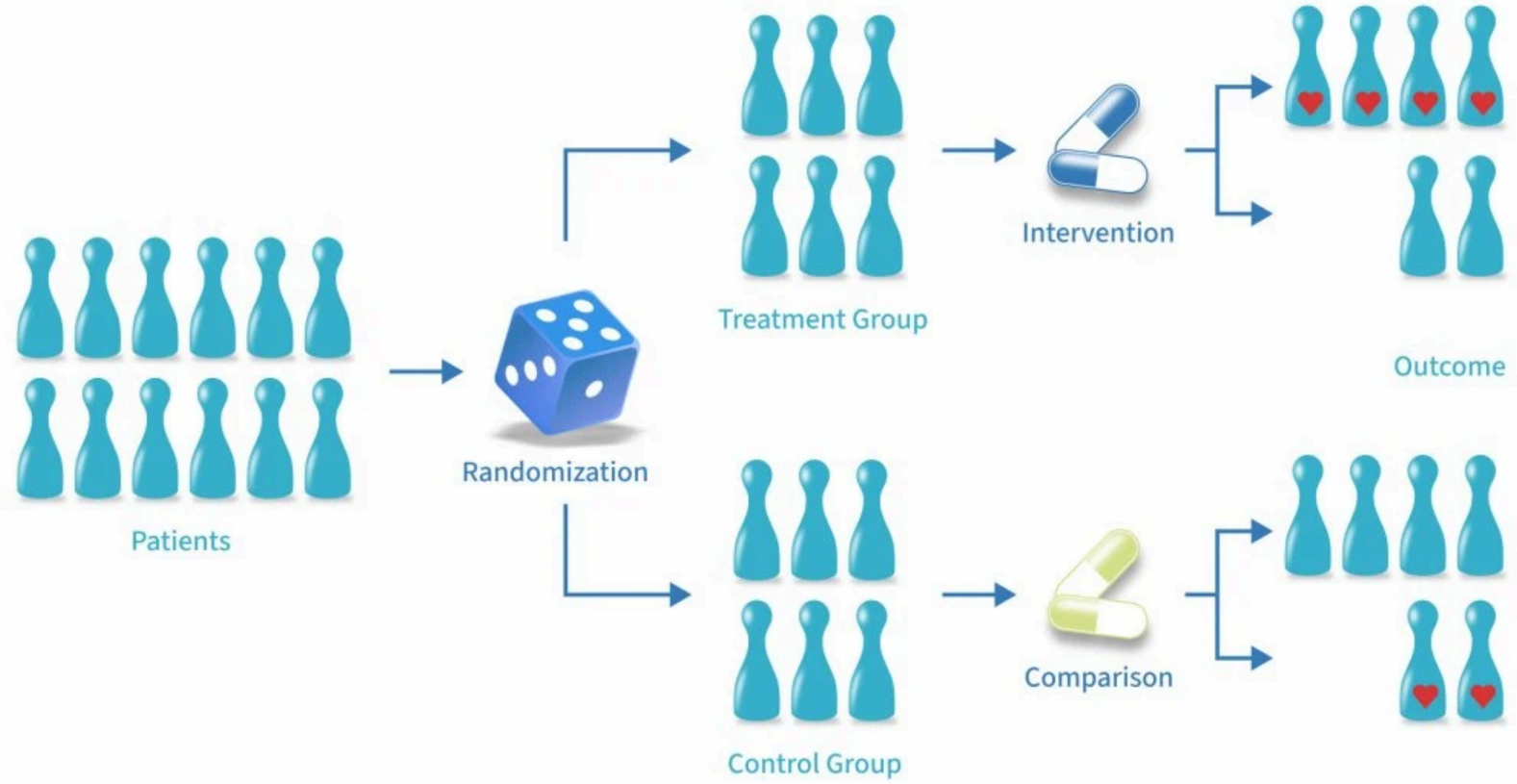

Associations
Seeing
What if I see ... ?
Interventions
Doing
What would I do ... ?
How?
Counterfactuals
Imagining
What if I had done ... ?
Why?

WHAT IF?

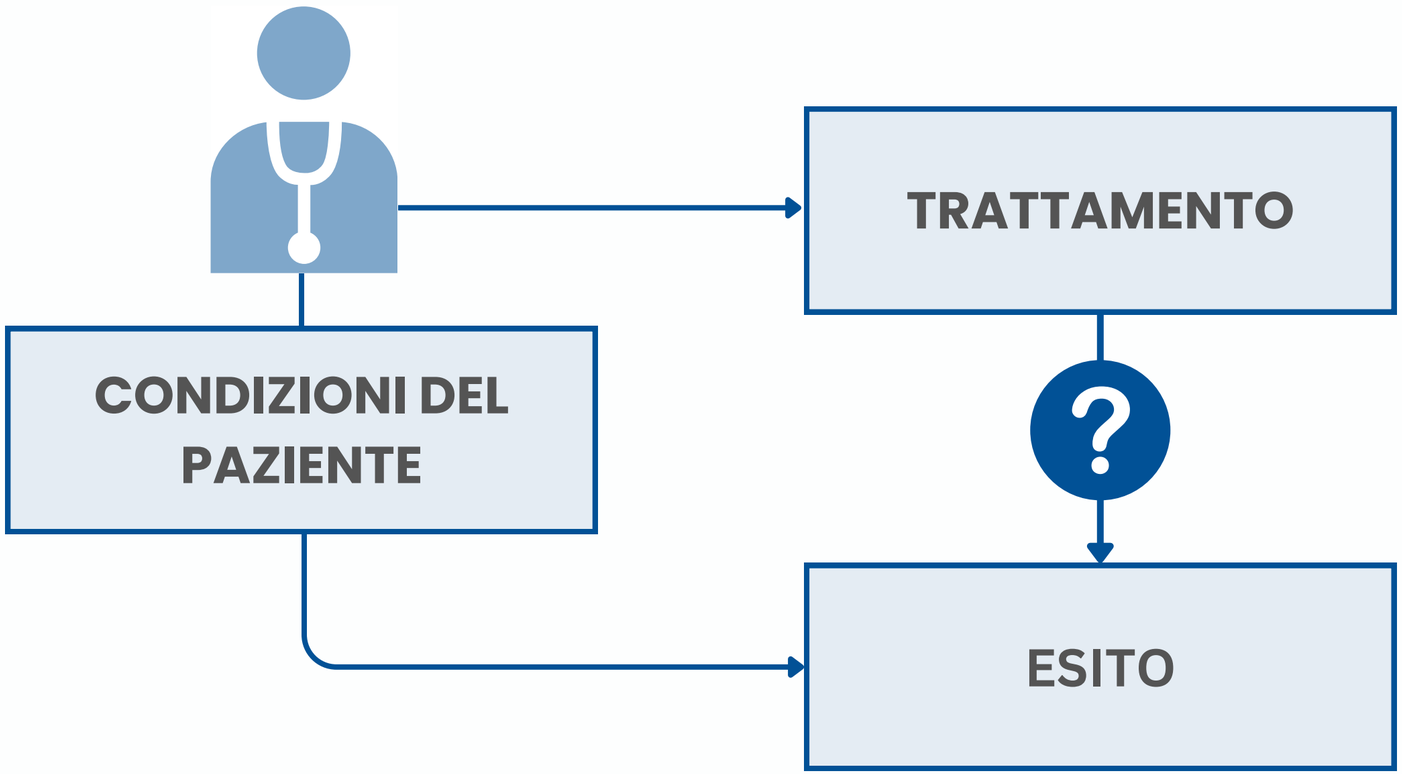

Amy's Depression Symptoms
BEFORE Treatment Assignment
Amy's Depression Symptoms
AFTER Treatment Assignment
$X_{i,t-1}$
$Y_{i,t}(0)$
$Y_{i,t}(1)$
?
Amy adopts a dog at time t-1
t-1
t
$W_{i,t-1}=1$
$\Delta=Y_{i,t}(1)-Y_{i,t}(0)$

COME?

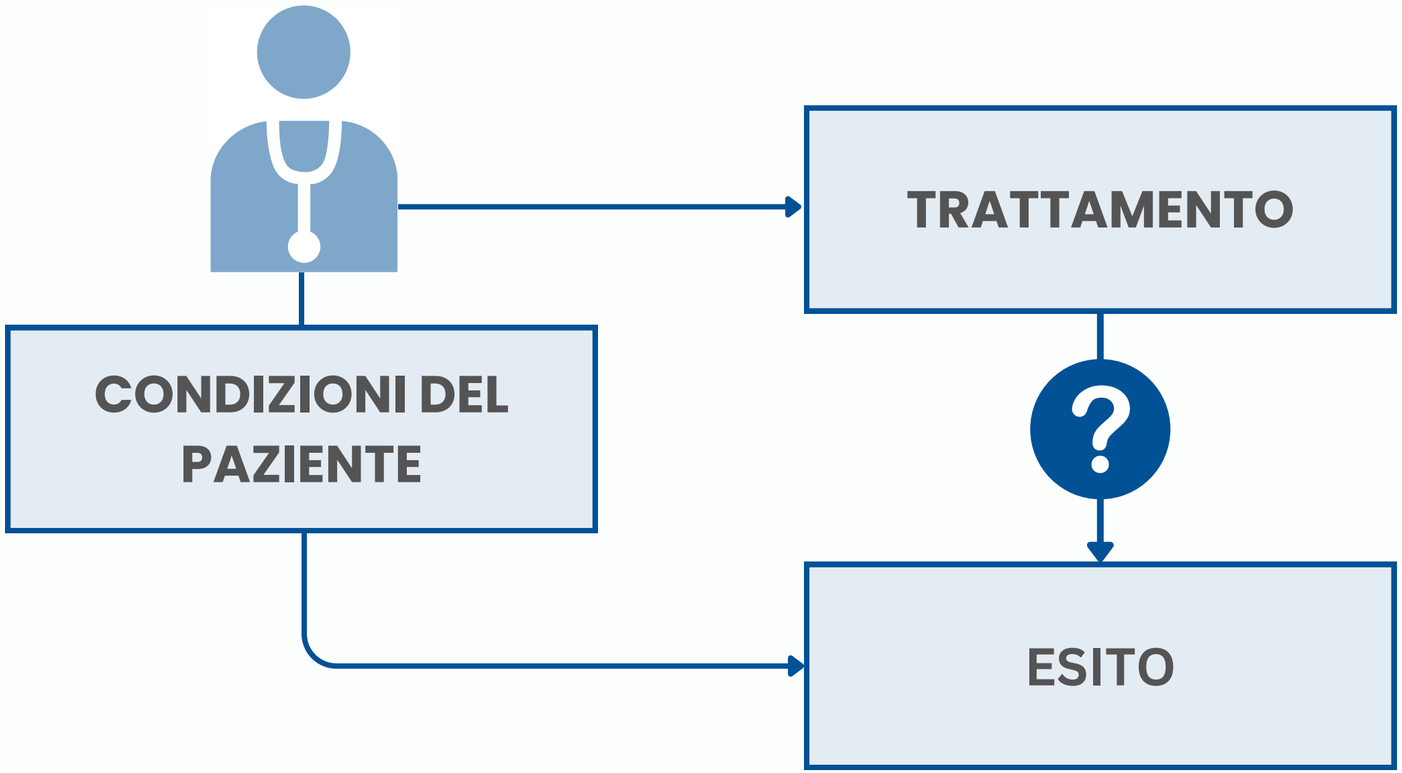
RANDOMIZED CONTROLLED TRIALS



STUDI OSSERVAZIONALI?

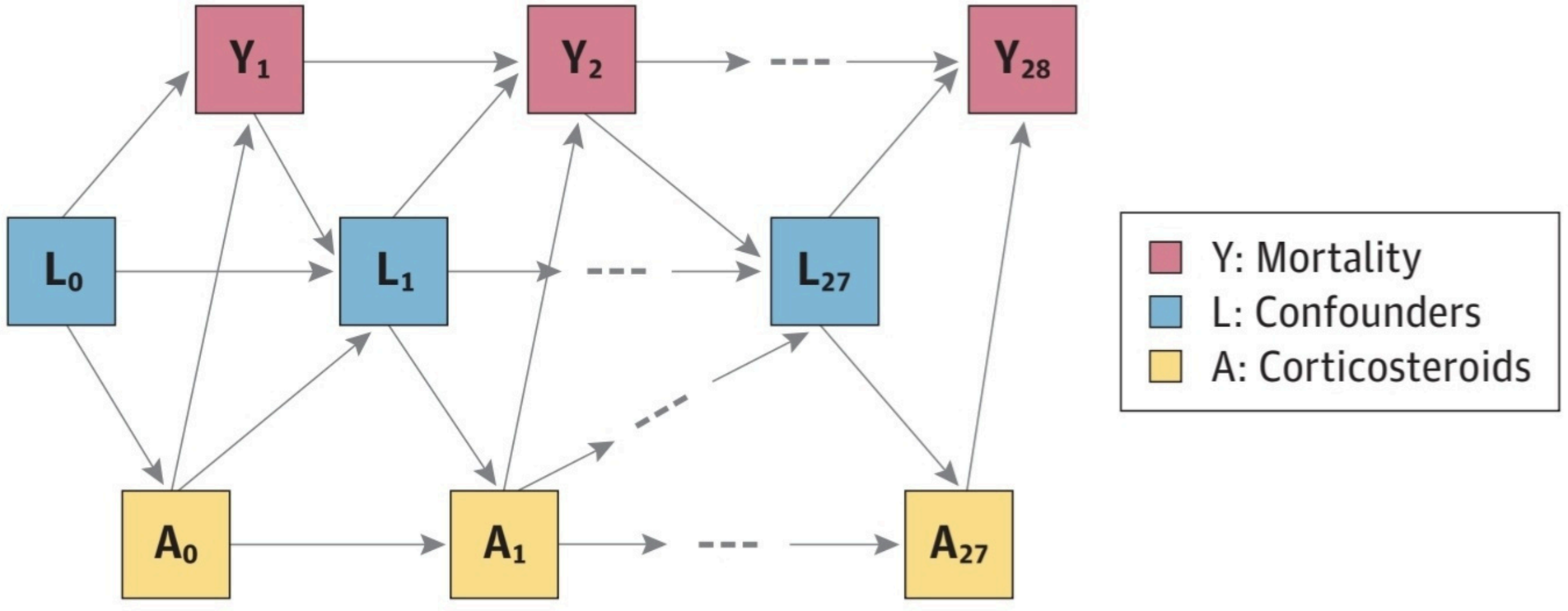


STUDI OSSERVAZIONALI?



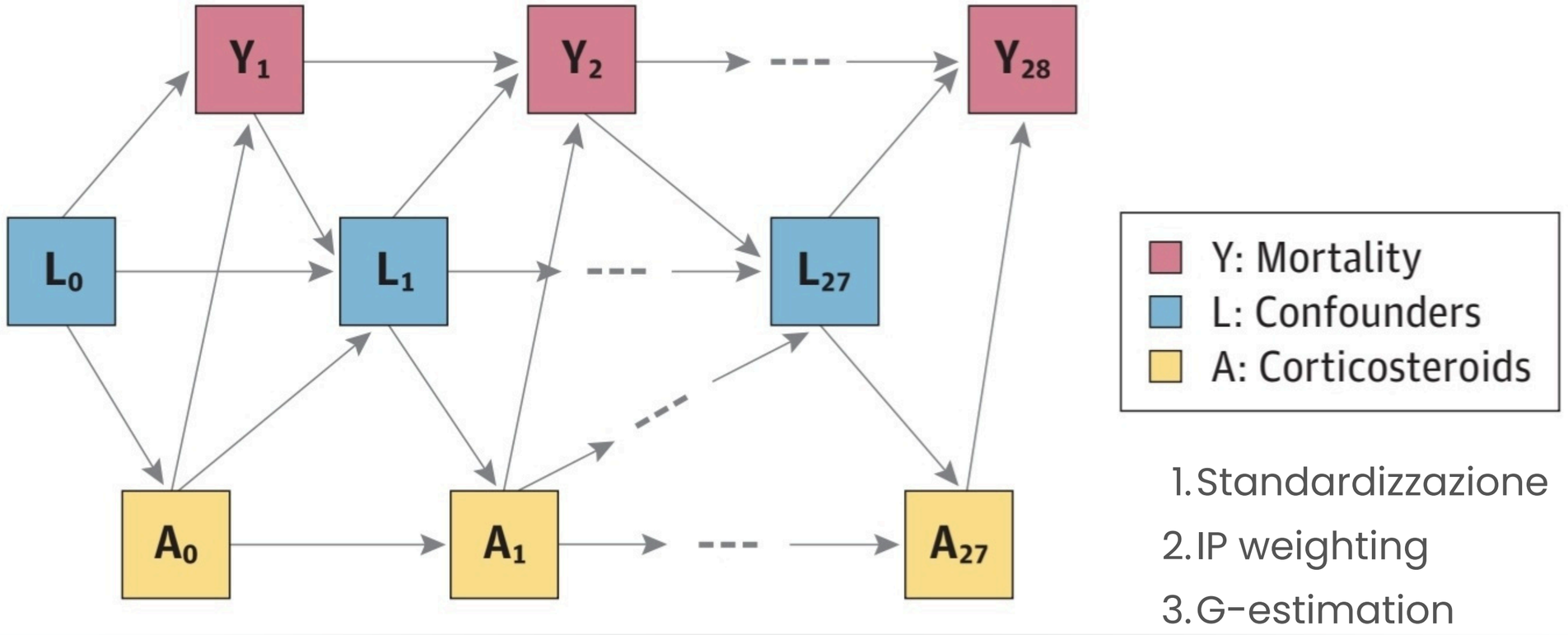
1. Regressione
2. Matching
3. Stratificazione
4. Standardizzazione
5. IP weighting
6. G-estimation

TRATTAMENTI TEMPO-DIPENDENTI



Hoffman, K. L., Schenck, E. J., Satlin, M. J., Whalen, W., Pan, D., Williams, N., & Díaz, I. (2022). Comparison of a target trial emulation framework vs Cox regression to estimate the association of corticosteroids with COVID-19 mortality. JAMA Network Open, 5(10), e2234425-e2234425.

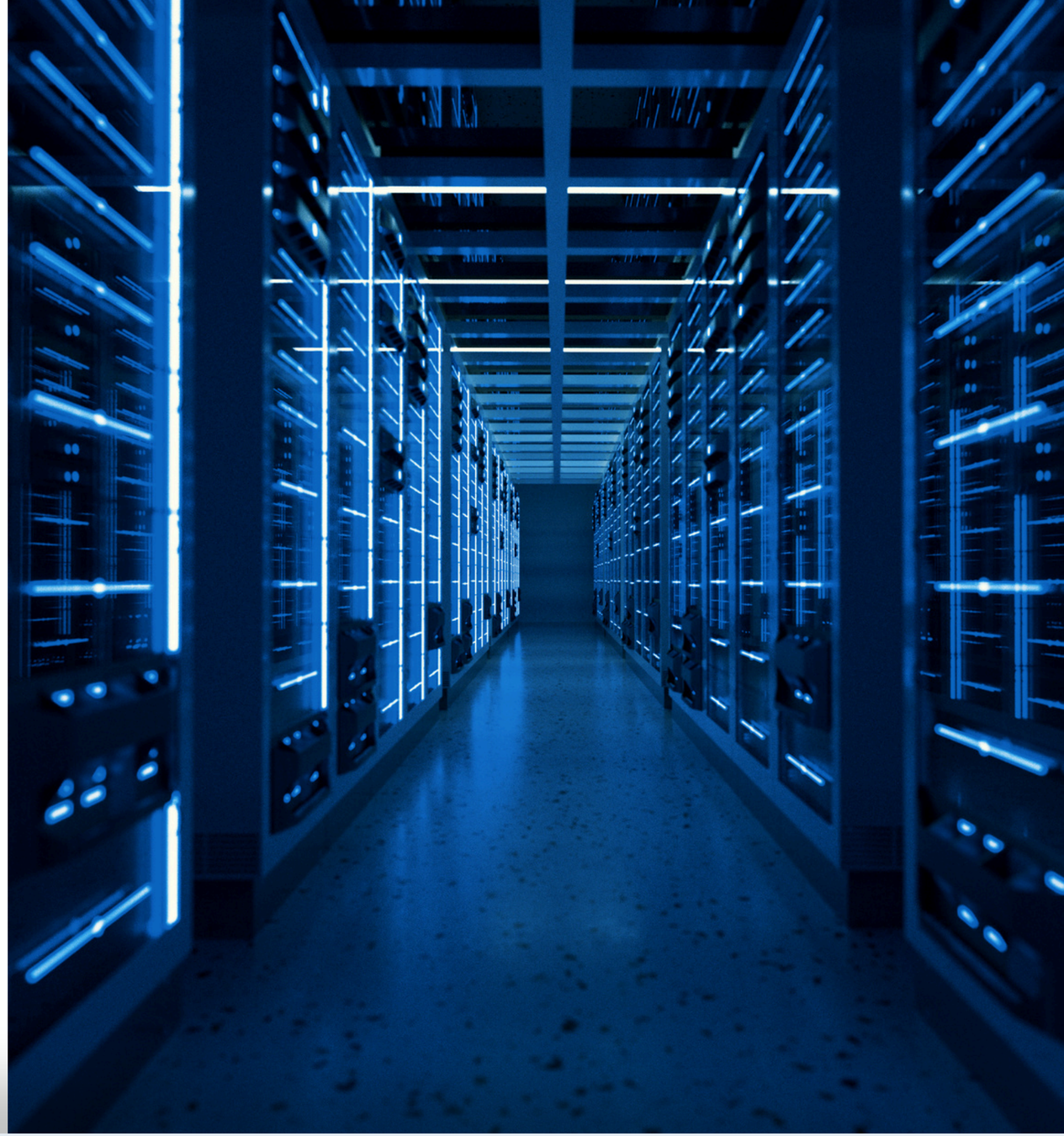
TRATTAMENTI TEMPO-DIPENDENTI



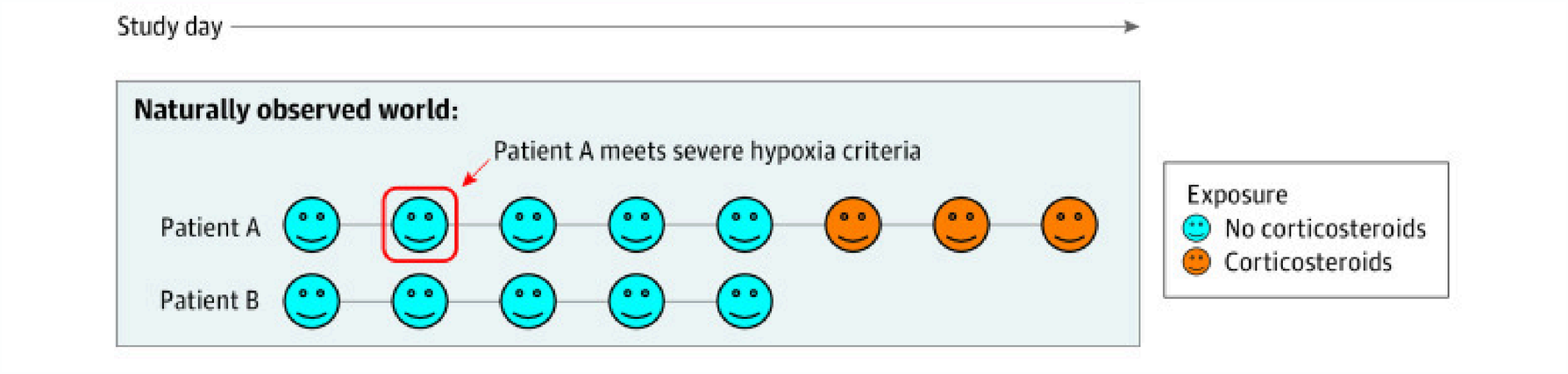
1. Standardizzazione
2. IP weighting
3. G-estimation

Hoffman, K. L., Schenck, E. J., Satlin, M. J., Whalen, W., Pan, D., Williams, N., & Díaz, I. (2022). Comparison of a target trial emulation framework vs Cox regression to estimate the association of corticosteroids with COVID-19 mortality. JAMA Network Open, 5(10), e2234425-e2234425.

EMULATED TARGET TRIALS



Hernán MA, Wang W, and Leaf DE (2022). Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA 328 (24), 2446-2447.



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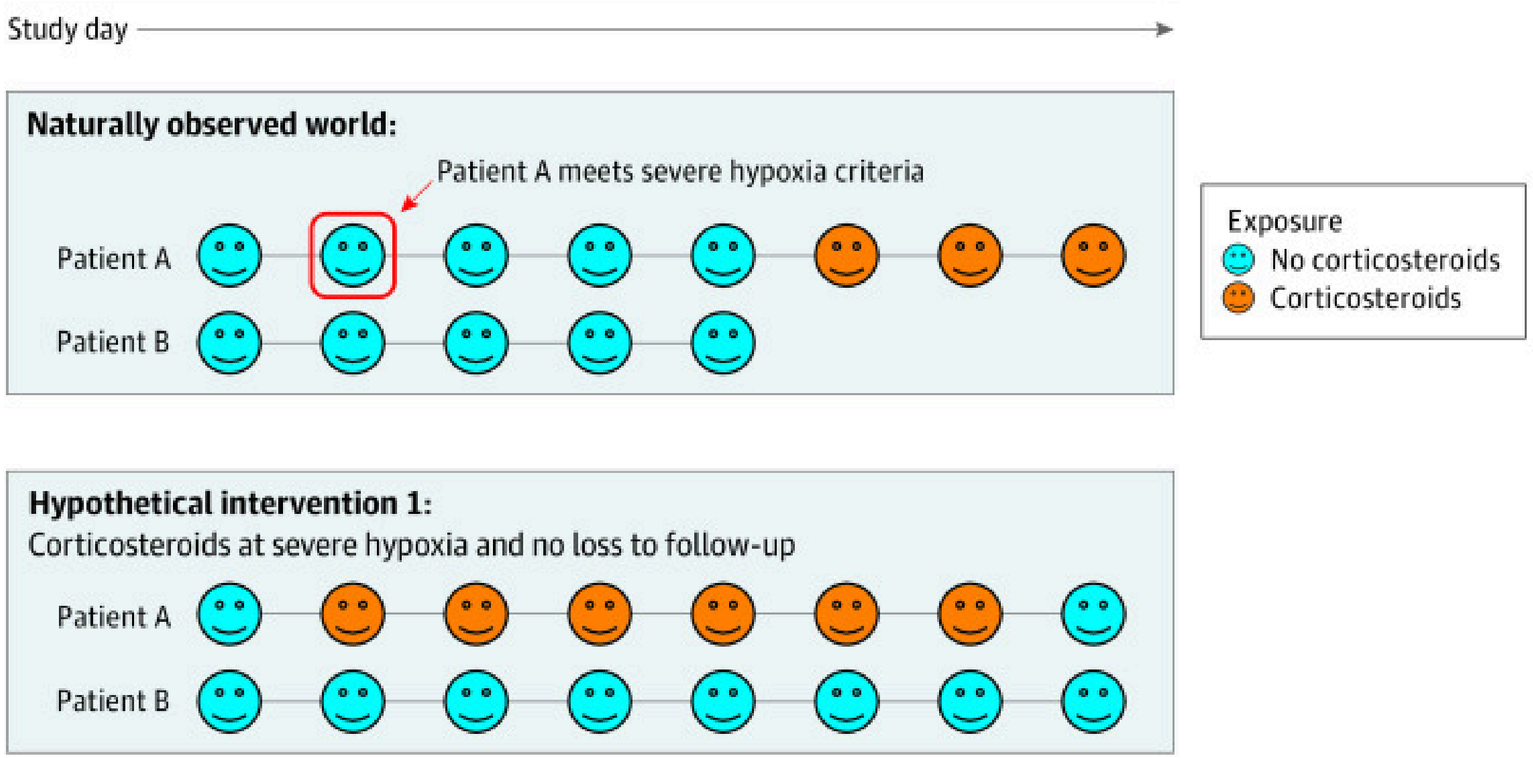

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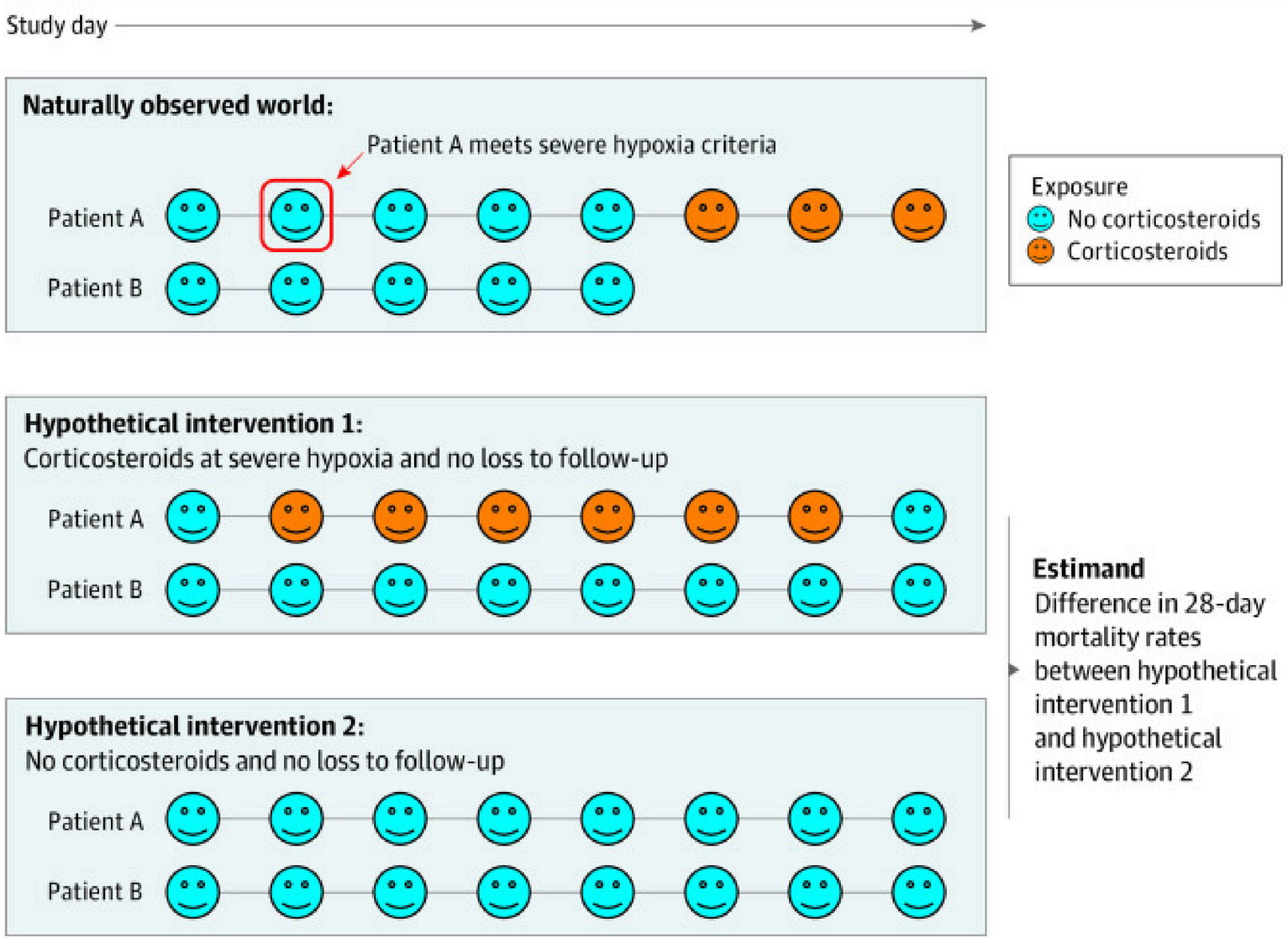

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avengARDS

EFFECTIVENESS OF LOW VOLUME AND LOW PRESSURE IN SEVERE HYPOXEMIC PATIENTS

ClinicalTrials.gov ID: NCT06513299

To obtain the dose-response curve of “lower VT” and “lower ΔP” in mechanically ventilated patients with acute severe hypoxemia.

The study set up to test the hypothesis that protective ventilatory settings able to minimize the risk of death due to VILI may be more effectively obtained targeting an optimal "lower" value of ΔP rather than an optimal value of "lower" of VT.

Clinical Trial > N Engl J Med. 2000 May 4;342(18):1301-8.

doi: 10.1056/NEJM200005043421801.

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome

Acute Respiratory Distress Syndrome Network; Roy G Brower, Michael A Matthay, Alan Morris, David Schoenfeld, B Taylor Thompson, Arthur Wheeler

PMID: 10793162 DOI: 10.1056/NEJM200005043421801

Free article

Practice Guideline > Am J Respir Crit Care Med. 2017 May 1;195(9):1253-1263.

doi: 10.1164/rccm.201703-0548ST.

An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome

Eddy Fan, Lorenzo Del Sorbo, Ewan C Goligher, Carol L Hodgson, Laveena Munshi, Allan J Walkey, Neill K J Adhikari, Marcelo B P Amato, Richard Branson, Roy G Brower, Niall D Ferguson, Ognjen Gajic, Luciano Gattinoni, Dean Hess, Jordi Mancebo, Maureen O Meade, Daniel F McAuley, Antonio Pesenti, V Marco Ranieri, Gordon D Rubenfeld, Eileen Rubin, Maureen Seckel, Arthur S Slutsky, Daniel Talmor, B Taylor Thompson, Hannah Wunsch, Elizabeth Uleryk, Jan Brozek, Laurent J Brochard; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine

PMID: 28459336 DOI: 10.1164/rccm.201703-0548ST

- **6 ml/kg** mortalità **inferiore** a 12 ml/kg
- raccomandazione **4–8 ml/kg**

LETTER ▸ Am J Respir Crit Care Med. 2021 Mar 30;204(7):868–869. doi: 10.1164/rccm.202105-1320LE

The Dethroning of 6 ml/kg as the "Go-To" Setting in Acute Respiratory Distress Syndrome

Martin J Tobin [1,2,*]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC8528533 PMID: 34186011

> Intensive Care Med. 2023 Jul;49(7):727-759. doi: 10.1007/s00134-023-07050-7. Epub 2023 Jun 16.

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

Giacomo Grasselli [# 1 2], Carolyn S Calfee [# 3], Luigi Camporota [# 4 5], Daniele Poole [6], Marcelo B P Amato [7], Massimo Antonelli [8 9], Yaseen M Arabi [10 11 12], Francesca Baroncelli [13], Jeremy R Beitler [14], Giacomo Bellani [15 16], Geoff Bellingan [17], Bronagh Blackwood [18], Lieuwe D J Bos [19], Laurent Brochard [20 21], Daniel Brodie [22], Karen E A Burns [21 23 24 25], Alain Combes [26 27], Sonia D'Arrigo [8], Daniel De Backer [28], Alexandre Demoule [29 30], Sharon Einav [31], Eddy Fan [21], Niall D Ferguson [32 33], Jean-Pierre Frat [34 35], Luciano Gattinoni [36], Claude Guérin [37 38], Margaret S Herridge [39], Carol Hodgson [40 41], Catherine L Hough [42], Samir Jaber [43], Nicole P Juffermans [44], Christian Karagiannidis [45], Jozef Kesecioglu [46], Arthur Kwizera [47], John G Laffey [48 49], Jordi Mancebo [50], Michael A Matthay [51], Daniel F McAuley [18 52], Alain Mercat [53], Nuala J Meyer [54], Marc Moss [55], Laveena Munshi [56], Sheila N Myatra [57], Michelle Ng Gong [58 59], Laurent Papazian [60 61], Bhakti K Patel [62], Mariangela Pellegrini [63], Anders Perner [64], Antonio Pesenti [65 66], Lise Piquilloud [67], Haibo Qiu [68], Marco V Ranieri [69 70], Elisabeth Riviello [71], Arthur S Slutsky [21 24], Renee D Stapleton [72], Charlotte Summers [73], Taylor B Thompson [74], Carmen S Valente Barbas [75 76], Jesús Villar [24 77 78], Lorraine B Ware [79], Björn Weiss [80], Fernando G Zampieri [81 82], Elie Azoulay [83], Maurizio Cecconi [84 85];
European Society of Intensive Care Medicine Taskforce on ARDS

Affiliations + expand

PMID: 37326646 PMCID: PMC10354163 DOI: 10.1007/s00134-023-07050-7

- **6 ml/kg non** superiore a valori fra 6 e 12 ml/kg
- **4–8 ml/kg non** supportato da significatività statistica

Observational Study > N Engl J Med. 2015 Feb 19;372(8):747-55.
doi: 10.1056/NEJMsa1410639.

Driving pressure and survival in the acute respiratory distress syndrome

Marcelo B P Amato [1], Maureen O Meade, Arthur S Slutsky, Laurent Brochard, Eduardo L V Costa, David A Schoenfeld, Thomas E Stewart, Matthias Briel, Daniel Talmor, Alain Mercat, Jean-Christophe M Richard, Carlos R R Carvalho, Roy G Brower

Affiliations + expand

PMID: 25693014 DOI: 10.1056/NEJMsa1410639

Free article

Randomized Controlled Trial > Am J Respir Crit Care Med. 2021 Jun 1;203(11):1378-1385.
doi: 10.1164/rccm.202009-3536OC.

Effect of Lowering Vt on Mortality in Acute Respiratory Distress Syndrome Varies with Respiratory System Elastance

Ewan C Goligher [1 2 3], Eduardo L V Costa [4 5], Christopher J Yarnell [1 6 2], Laurent J Brochard [1 7], Thomas E Stewart [8], George Tomlinson [2], Roy G Brower [9], Arthur S Slutsky [1 7], Marcelo P B Amato [4]

Affiliations + expand

PMID: 33439781 DOI: 10.1164/rccm.202009-3536OC

- normalizzazione VT/peso misleading per pazienti a bassa compliance
- ΔP parametro indice di effetto protettivo

> Intensive Care Med. 2005 Jun;31(6):776-84. doi: 10.1007/s00134-005-2627-z. Epub 2005 Apr 6.

The concept of "baby lung"

Luciano Gattinoni [1], Antonio Pesenti

Affiliations + expand

PMID: 15812622 DOI: 10.1007/s00134-005-2627-z

Clinical Trial > Am J Respir Crit Care Med. 2007 Jan 15;175(2):160-6.
doi: 10.1164/rccm.200607-915OC. Epub 2006 Oct 12.

Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome

Pier Paolo Terragni [1], Giulio Rosboch, Andrea Tealdi, Eleonora Corno, Eleonora Menaldo, Ottavio Davini, Giovanni Gandini, Peter Herrmann, Luciana Mascia, Michel Quintel, Arthur S Slutsky, Luciano Gattinoni, V Marco Ranieri

Affiliations + expand

PMID: 17038660 DOI: 10.1164/rccm.200607-915OC

Limiting Dynamic Driving Pressure in Patients Requiring Mechanical Ventilation*

OBJECTIVES: Previous studies reported an association between higher driving pressure (ΔP) and increased mortality for different groups of mechanically ventilated patients. However, it remained unclear if sustained intervention on ΔP, in addition to traditional lung-protective ventilation, improves outcomes. We investigated if ventilation strategies limiting daily static or dynamic ΔP reduce mortality compared with usual care in adult patients requiring greater than or equal to 24 hours of mechanical ventilation.

DESIGN: For this comparative effectiveness study, we emulated pragmatic clinical trials using data from the Toronto Intensive Care Observational Registry re-

Martin Urner, MD, PhD[1–3]

Peter Jüni, MD, FESC[3–6]

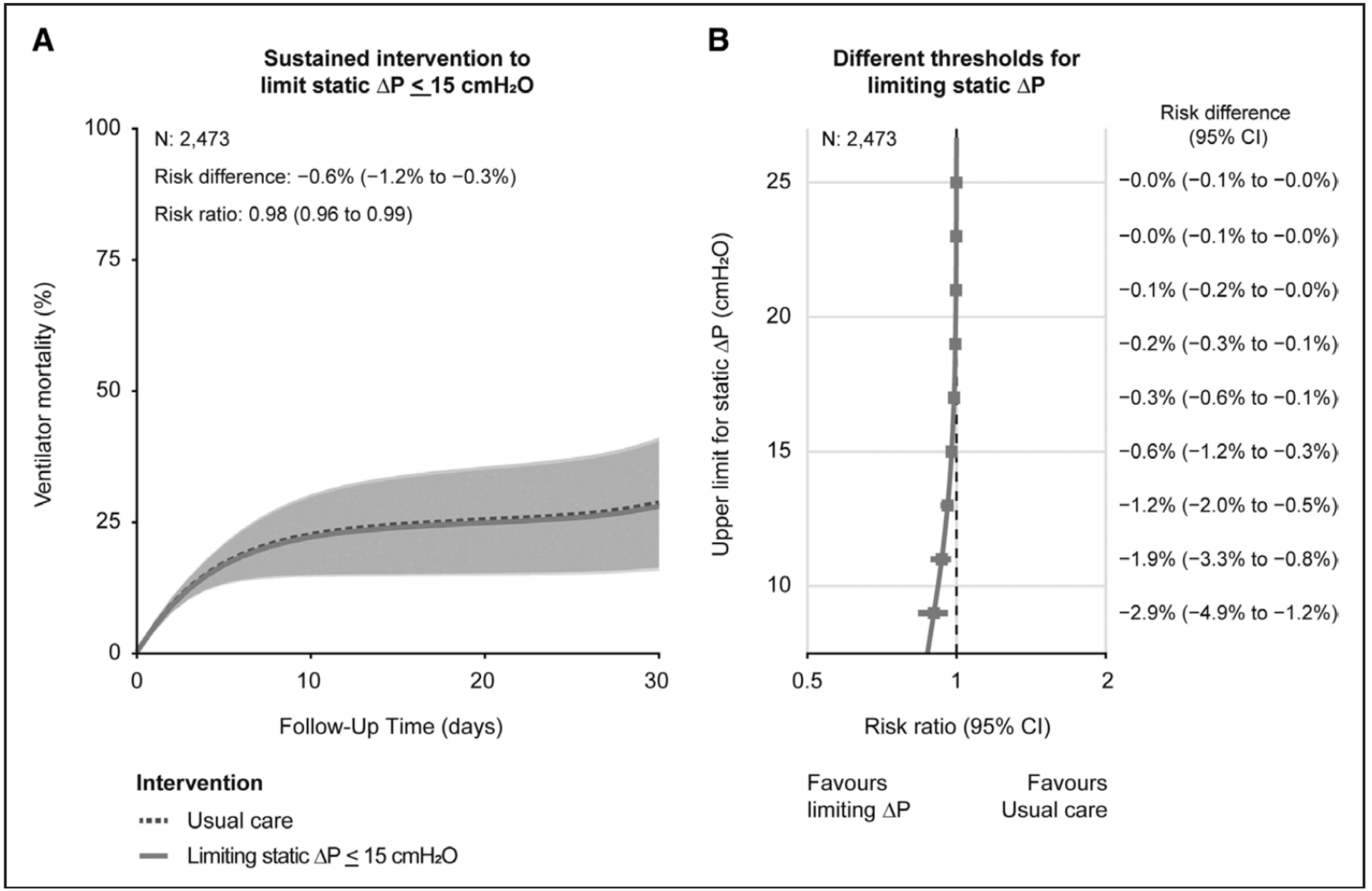
L. Paloma Rojas-Saunero, MD, PhD[7]

Bettina Hansen, PhD[3,8]

Laurent J. Brochard, MD, HDR[1,4,5]

Niall D. Ferguson, MD, MSc[1,3,4,8–10]

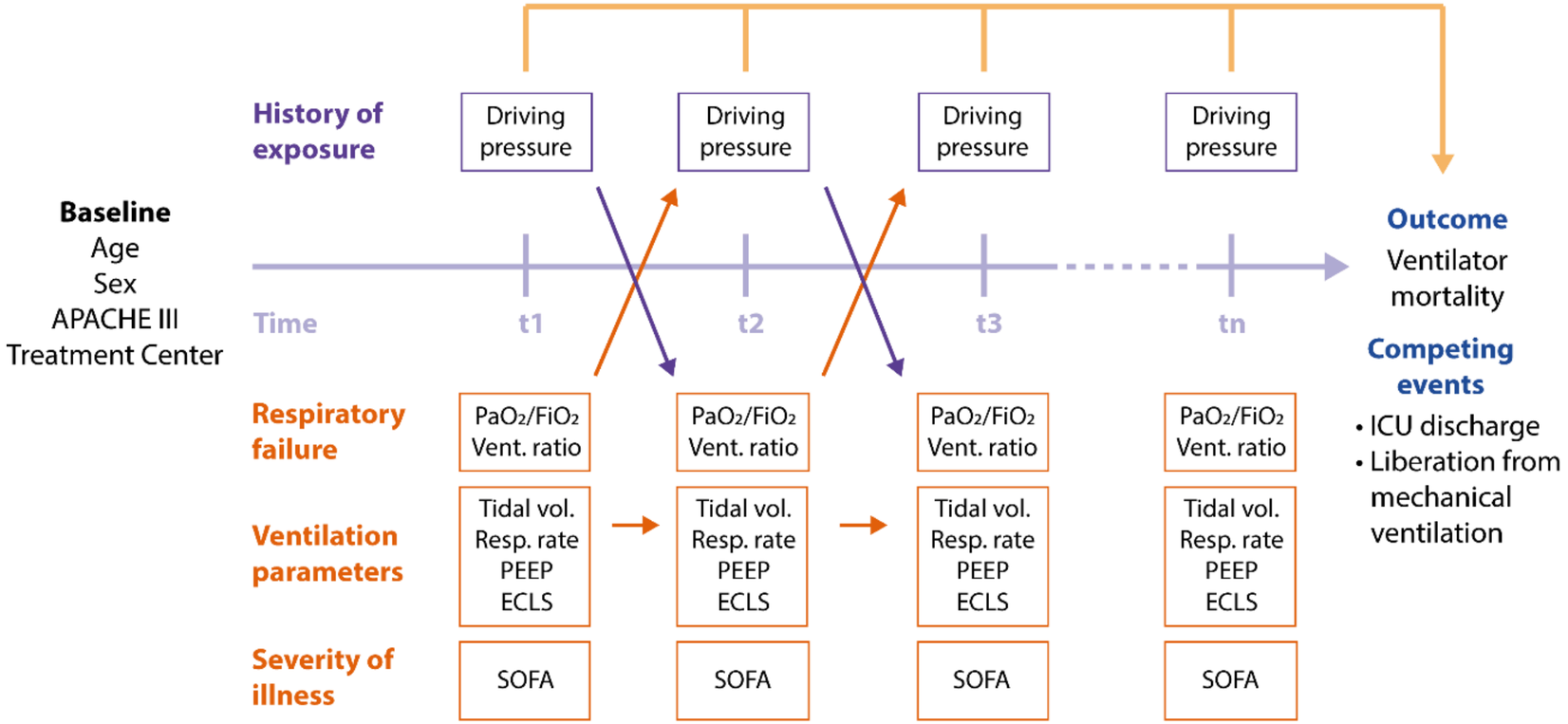
Eddy Fan, MD, PhD[1,3,4,8,10]



Urner, M., Jüni, P., Rojas-Saunero, L. P., Hansen, B., Brochard, L. J., Ferguson, N. D., & Fan, E. (2023). Limiting dynamic driving pressure in patients requiring mechanical ventilation. Critical care medicine, 51(7), 861-871.

Sustained intervention on driving pressure

The causal effect of the intervention can only be estimated under full adherence in an observational analogue of a per-protocol analysis. The effect of driving pressure can me **mediated** and **confounded** by time-varying variables, such as the degree of respiratory failure, ventilation parameters, or the severity of illness.



Time-varying confounders affected by previous treatment

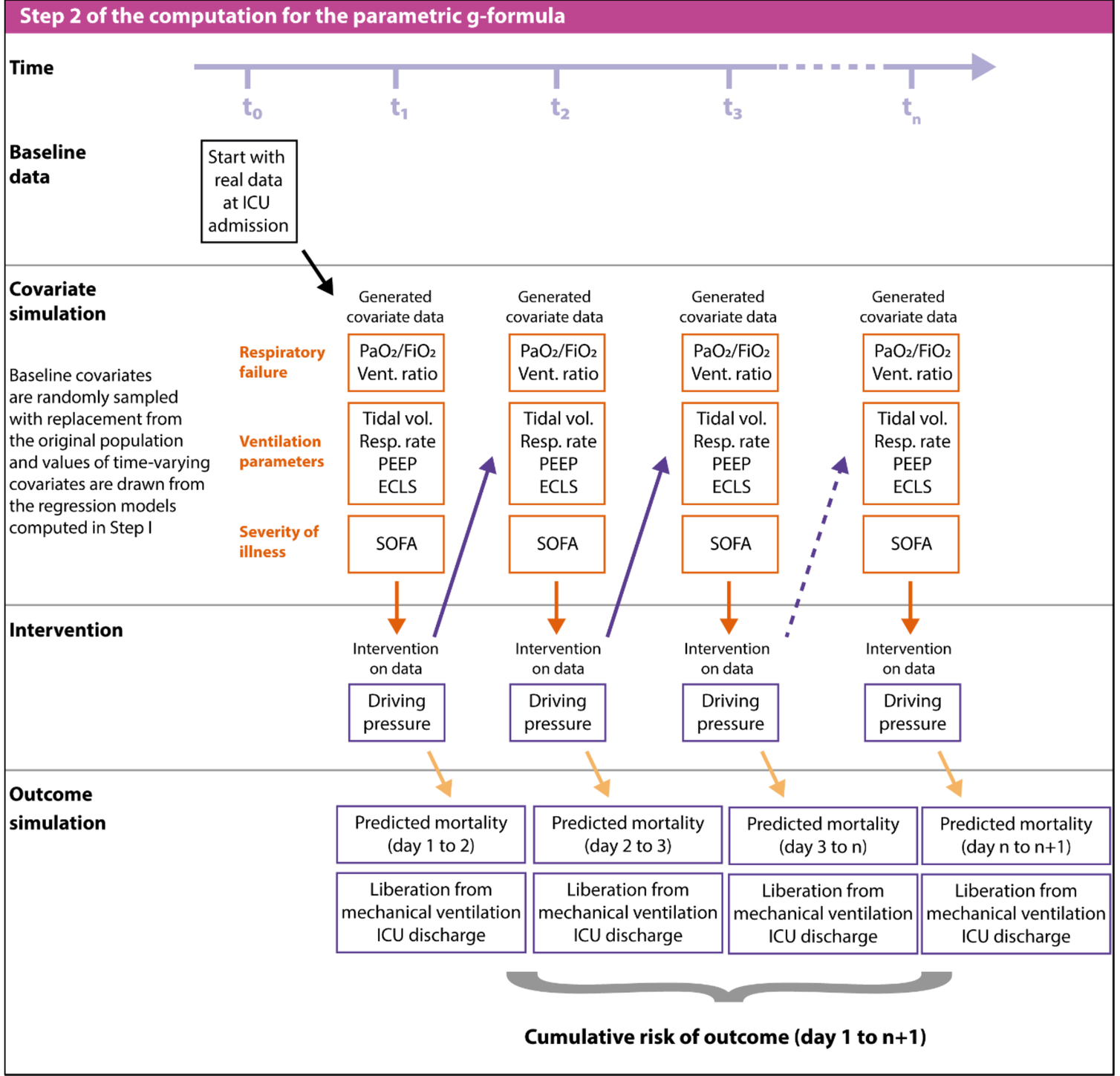
Time-varying variables, such as the degree of respiratory failure, ventilation parameters, or the severity of illness, act as **confounders** and **intermediate variables** at the same time. Traditional methods, such as standard regression models, cannot be used to calculate adherence-adjusted estimates as they can introduce bias (e.g., over-adjustment bias, collider-stratification bias)

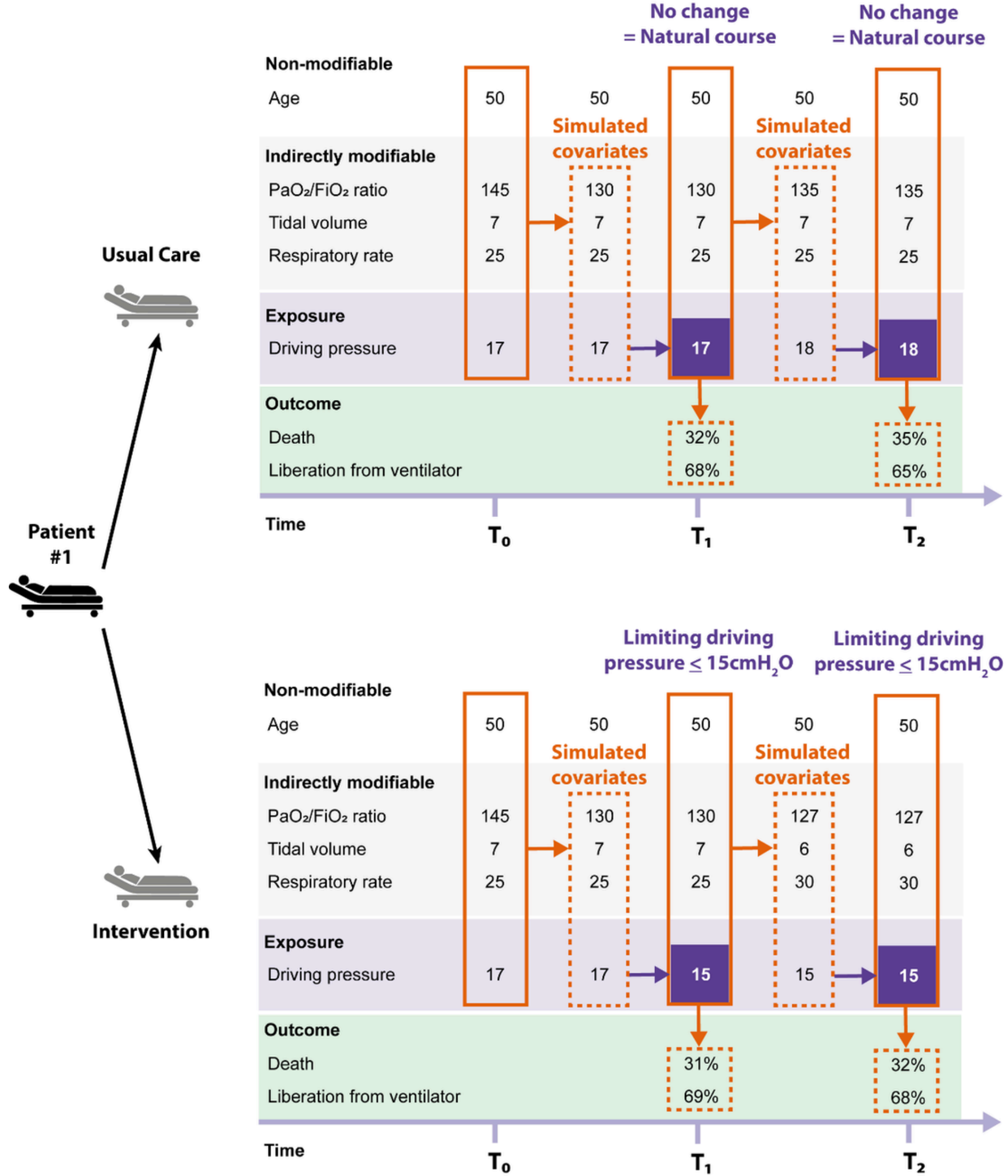
Differential censoring

The effect of an intervention on driving pressure on outcome can be mediated by an effect of driving pressure on the competing event.

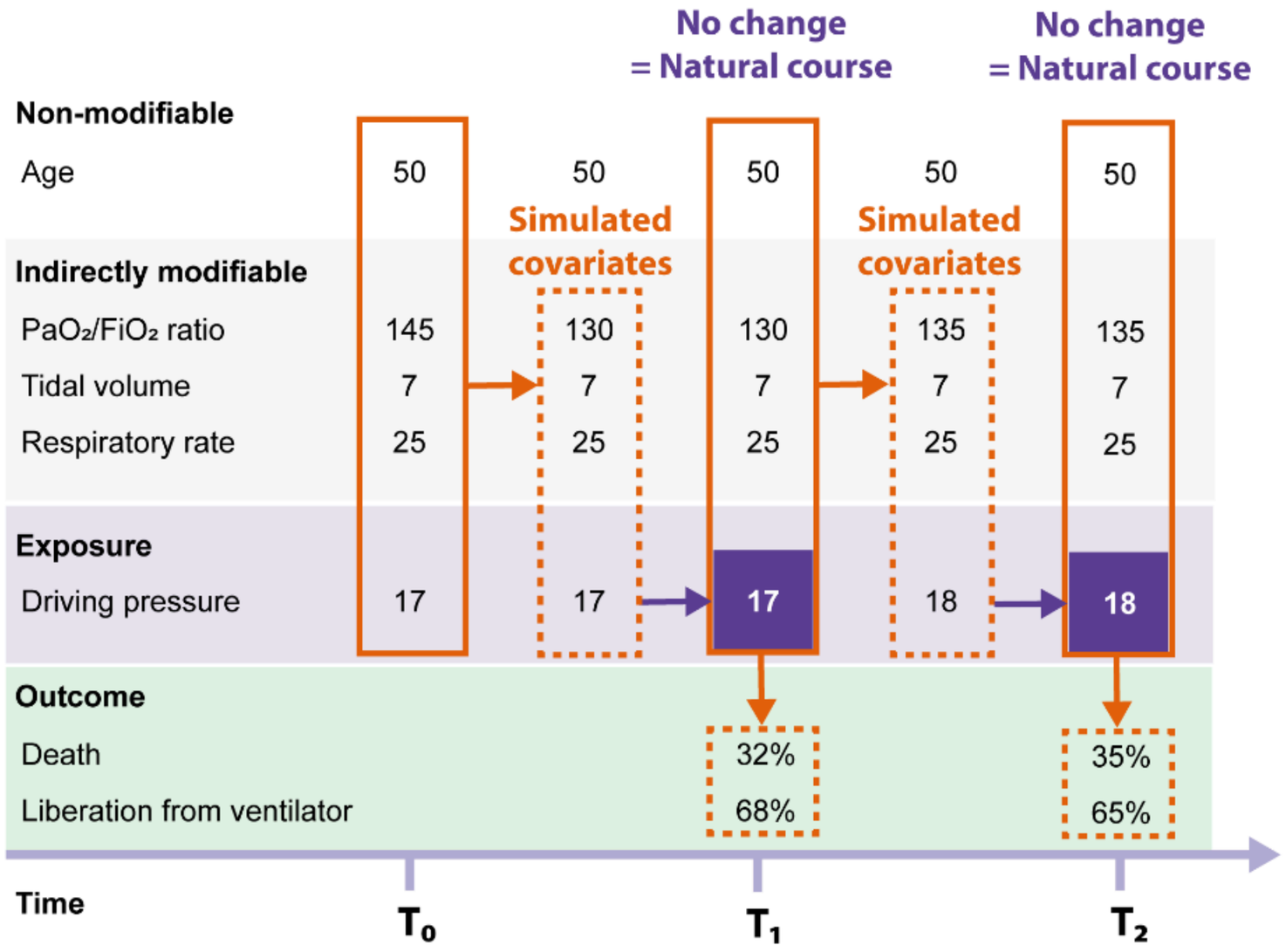
g-ESTIMATION

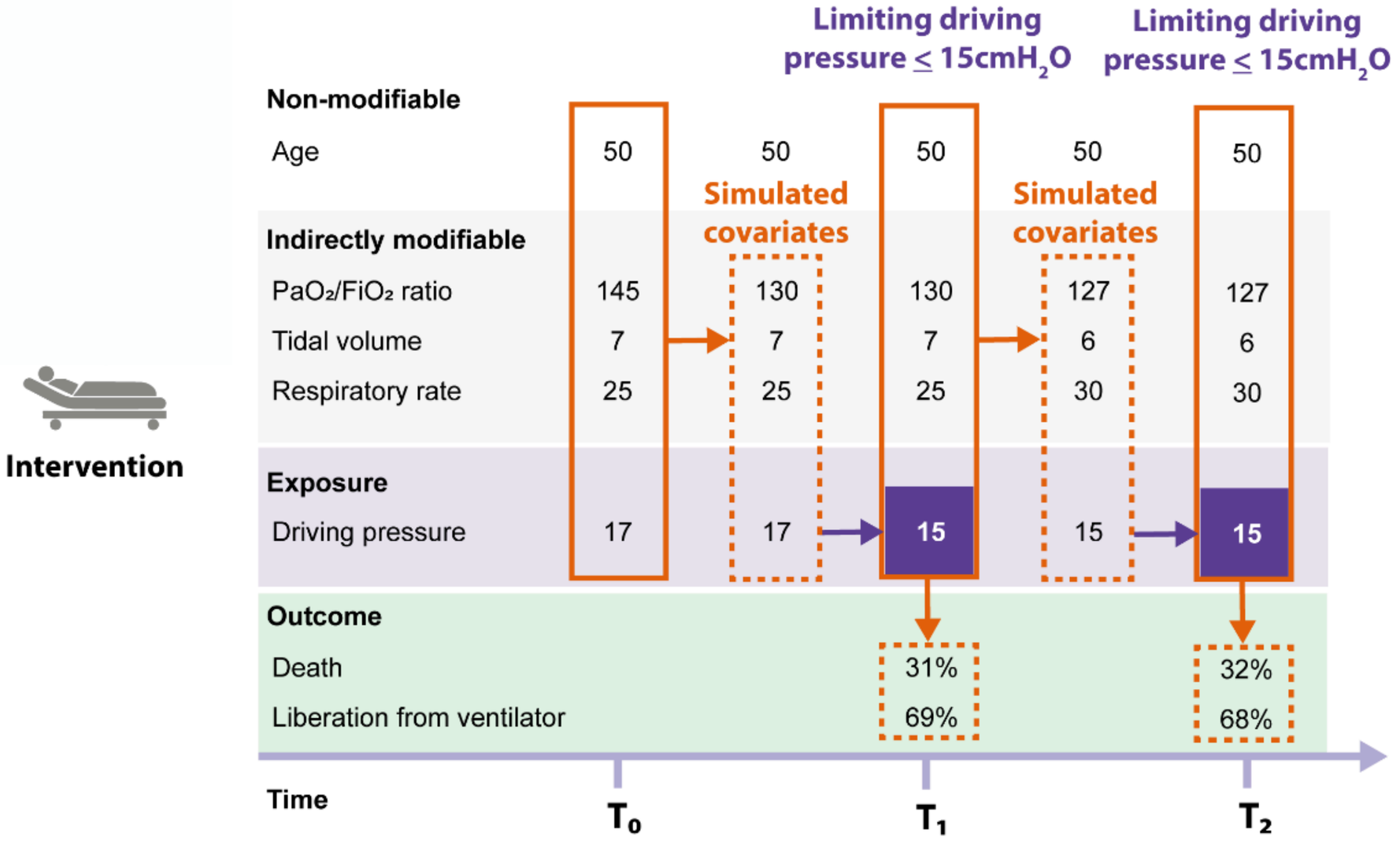
Step 1	Step 2	Step 3
Fit parametric regression models for each of the time-varying covariates, as a function of prior risk factor history at each time point.	Simulate the course in the ICU for a large pseudopopulation of patients under the treatment strategy of interest.	Use bootstrap methods to obtain 95% confidence intervals for the estimated risks of outcomes and measures of comparison between the interventions


Step 2 of the computation for the parametric g-formula
Time
t_0
t_1
t_2
t_3
t_n
Baseline data
Start with real data at ICU admission
Covariate simulation
Baseline covariates are randomly sampled with replacement from the original population and values of time-varying covariates are drawn from the regression models computed in Step I
Respiratory failure
Ventilation parameters
Severity of illness
Generated covariate data
PaO2/FiO2 Vent. ratio
Tidal vol. Resp. rate PEEP ECLS
SOFA
Intervention
Intervention on data
Driving pressure
Outcome simulation
Predicted mortality (day 1 to 2)
Predicted mortality (day 2 to 3)
Predicted mortality (day 3 to n)
Predicted mortality (day n to n+1)
Liberation from mechanical ventilation ICU discharge
Cumulative risk of outcome (day 1 to n+1)


Usual Care
Patient #1
Intervention
No change = Natural course
No change = Natural course
Non-modifiable
Age
50
50
50
50
50
Simulated covariates
Simulated covariates
Indirectly modifiable
PaO2/FiO2 ratio
145
130
130
135
135
Tidal volume
7
7
7
7
7
Respiratory rate
25
25
25
25
25
Exposure
Driving pressure
17
17
17
18
18
Outcome
Death
32%
35%
Liberation from ventilator
68%
65%
Time
T0
T1
T2
Limiting driving pressure ≤ 15cmH2O
Limiting driving pressure ≤ 15cmH2O
Non-modifiable
Age
50
50
50
50
50
Simulated covariates
Simulated covariates
Indirectly modifiable
PaO2/FiO2 ratio
145
130
130
127
127
Tidal volume
7
7
7
6
6
Respiratory rate
25
25
25
30
30
Exposure
Driving pressure
17
17
15
15
15
Outcome
Death
31%
32%
Liberation from ventilator
69%
68%
Time
T0
T1
T2

Usual Care


No change
= Natural course
No change
= Natural course
Non-modifiable
Age
50
50
50
50
50
Simulated covariates
Simulated covariates
Indirectly modifiable
PaO₂/FiO₂ ratio
145
130
130
135
135
Tidal volume
7
7
7
7
7
Respiratory rate
25
25
25
25
25
Exposure
Driving pressure
17
17
17
18
18
Outcome
Death
32%
35%
Liberation from ventilator
68%
65%
Time
T₀
T₁
T₂


Limiting driving pressure ≤ 15cmH2O
Limiting driving pressure ≤ 15cmH2O
Non-modifiable
Age
50
50
50
50
50
Simulated covariates
Simulated covariates
Indirectly modifiable
PaO2/FiO2 ratio
145
130
130
127
127
Tidal volume
7
7
7
6
6
Respiratory rate
25
25
25
30
30
Exposure
Driving pressure
17
17
15
15
15
Outcome
Death
31%
32%
Liberation from ventilator
69%
68%
Time
T0
T1
T2
Intervention

avengARDS

NCT06513299

- protocollo riformulato dati real-life MargheritaTre
- no immagini, referti non strutturati/standardizzati
- ARDS -> Ipossiemia Acuta

	TARGET TRIAL	TARGET TRIAL EMULATION
Inclusion Criteria	ALL THE FOLLOWINGS: (a) age ≥ 18 years. (b) all the following conditions present continuously for 24 hours commencing within 36 hours of ICU admission, while the patient is undergoing invasive mechanical ventilation in either flow or pressure-regulated assist/controlled modes: a. arterial oxygen tension (PaO2) to inspiratory oxygen fraction (FiO2) ratio P/F ≤ 300 mmHg b. hypoxemia developed within one week of a known clinical insult c. hypoxemia not fully explained by cardiac failure or fluid overload*	(a) same as TT (b) same as TT*

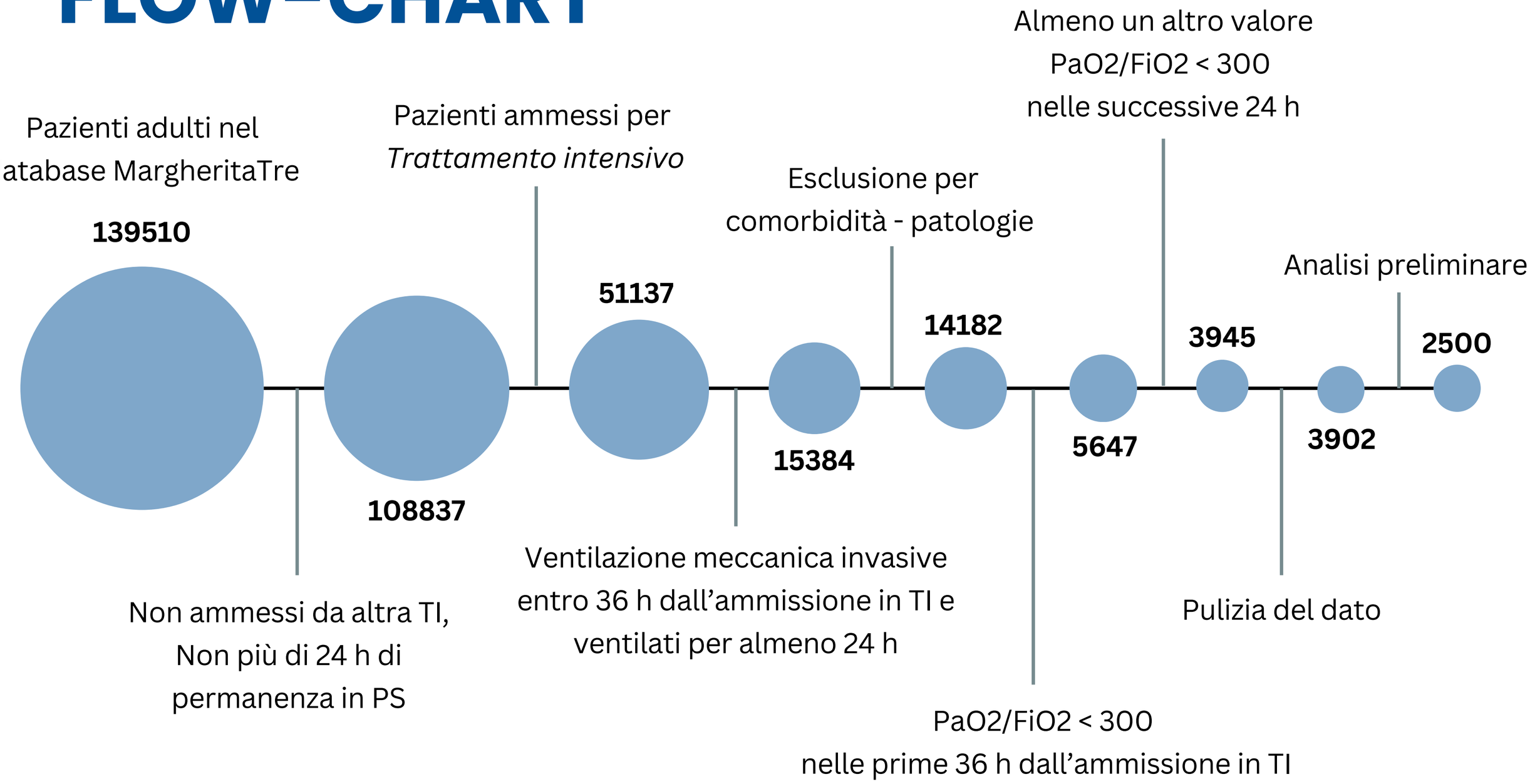
Exclusion Criteria	ANY OF THE FOLLOWINGS: (a) pregnancy (b) expected duration of mechanical ventilation < 48h (c) severe or moderate COPD (d) chronic liver disease (e) acute brain injury (f) patient admitted for palliative sedation (g) tumor with metastases (h) prior cardiac arrest (i) New York Heart Association Class IV (j) acute coronary syndrome (k) patients transferred from other ICUs (l) patients transferred to the ICU from the Emergency Department after a duration exceeding 24 hours in the Emergency Department (m) patients on Pressure Support Ventilation and/or patients in whom end-inspiratory plateau pressure was not measured	(a) same as TT* (b) same as TT* (c) same as TT* (d) same as TT* (e) same as TT* (f) same as TT* (g) same as TT* (h) same as TT* (i) same as TT*

Treatment strategies	Mode of mechanical ventilation: constant flow/constant pressure, assist/control; RR up to 35 bpm. PEEP will be set according to clinical judgement. Predicted Body Weight (PBW) will be calculated according to the following formulae: **PBW (Males)** = 50+0.91 [height (cm)-152.4]; **PBW (Females)** = 45.5 + 0.91 height (cm)-152.4]. Oxygenation Goal: PaO_2 55-80 mmHg or SpO_2 88-95%; Arterial pH Goal: 7.30-7.45. ***TIDAL VOLUME*** ***GUIDED PROTECTIVE VENTILATION*** Tidal volume (V_T) will be set to: **Arm VT 1.** V_T 6.0-8.0 ml/Kg PBW with $P_{PLAT} \leq 30$ cmH_2O; **Arm VT 2.** V_T 8.1-11.9 ml/Kg PBW with $P_{PLAT} \leq 30$ cmH_2O ***DRIVING PRESSURE*** ***GUIDED PROTECTIVE VENTILATION*** Driving pressure (ΔP) will be set to: **Arm ΔP1.** 10.0-15.0 cmH_2O; 15.1- 18.0 cmH_2O **Arm ΔP 2**15.1- 18.0 cmH_2O The value of V_T and ΔP in the corresponding arm interval is chosen according to clinical judgement. Intervention will be maintained until the patient will be considered eligible for respiratory weaning when all the following criteria will be met: ● (P/F) > 250 mmHg ● PEEP ≤ 8 cmH_2O and lower than the previous day ● FiO_2 < 0.5 and lower than the previous day ● systolic arterial pressure ≥ 85 mmHg without vasopressor or inotropic support (≤ 5 mcg/kg/min dopamine or dobutamine will not considered as inotropic support)	**Simulated interventions** For each treatment arm, the value of the continuous variable V_T (ΔP, respectively) is set equal to its natural value if the natural value is inside the range of the corresponding arm. Otherwise, it is set equal to the value at of the edge of the range which is closer to the natural value (e,g. For VT1, if the natural value of V_T is lower than 6 ml/kg PBW, the intervention value is set to 6 ml/kg PBW; if the natural value is greater than 8 ml/kg PBW, the intervention value is set to 8 ml/kg PBW), Treatment corresponding to the TT intervention is maintained until patient is eligible for respiratory weaning, then the natural value of treatment is applied (either no mechanical ventilation or ventilation with natural value of V_T or ΔP.

Treatment assignment	Randomization	Simulation of dynamic interventions on the same population
Primary End-Point	**ICU all-cause mortality:** All patients will be classified as either alive if *alive at ICU discharge* or dead if *dead during ICU stay*	Same as TT
Secondary End-Point	**Number of ventilator free-days during follow-up**	Same as TT
Secondary Analysis	• Dose response curve for V_T and ΔP • Comparison of best policy with fixed V_T versus best policy with fixed ΔP. Best policy is defined as the one with best treatment effect among those used in intervention arms.	• Treatment effect computed simulating a modified treatment policy with constant V_T and ΔP, respectively until conditions for weaning are satisfied, then natural value of treatment • Same as TT
Follow up	14 days after randomization	Same as TT
Causal Contrasts	**Intention-to-treat effect** Effect on study outcomes will be analyzed in those patients that were assigned to the treatment arm. **Per-protocol effect** Effect on study outcomes will be analyzed in those patients that effectively received the treatment (either tidal volume or driving pressure).	**Observation analogue of per-protocol effect** Effect on study outcomes will be analyzed using simulated treatment strategies.

Statistical Analysis	In the per-protocol analysis, patients will be censored when they deviated from their assigned strategy. The per-protocol effect will be estimated after adjustment for baseline variables and for time-varying variables associated with adherence to a ventilation strategy according the treatment arms. Subgroup analysis by previously selected baseline clinical (age, severity of ARDS, SAPS and SOFA scores) and physiological (quartiles of compliance, driving pressure, Plateau Pressure, ventilatory index) variables.	The per-protocol effect under full adherence will be estimated using the g-estimation methods. The value of each density function for all possible covariate histories was estimated under parametric modeling assumptions. **Confounders** **baseline:** demographics, comorbidities, organ failure and clinical conditions at ICU admission, components of SAPS and SOFA scores **time varying:** P/F, PEEP, FiO_2, systolic and mean arterial pressure, vasoactive and inotropic drugs, components of SOFA score **Competing events** ICU discharge prior to end of follow-up Subgroup analysis same as the target trial
Sensitivity Analysis	• Same inclusion criteria but no exclusion criteria • patients satisfying radiological criteria for ARDS • patients ventilated in flow regulated assist/controlled modes vs. patients ventilated with pressure-regulated assist/controlled modes • P/F 300-200 vs. P/F 200-100 vs. P/F < 100 • quartiles of static compliance • quartiles of dynamic compliance • quartiles of peak pressure • quartiles of static pressure • quartiles of mechanical power • presence of inclusion criteria (c) starting from within 12 hours from ICU admission	• Same as TT

FLOW-CHART


Pazienti adulti nel database MargheritaTre
139510
Non ammessi da altra TI, Non più di 24 h di permanenza in PS
108837
Pazienti ammessi per *Trattamento intensivo*
51137
Ventilazione meccanica invasive entro 36 h dall'ammissione in TI e ventilati per almeno 24 h
15384
Esclusione per comorbidità - patologie
14182
PaO2/FiO2 < 300 nelle prime 36 h dall'ammissione in TI
5647
Almeno un altro valore PaO2/FiO2 < 300 nelle successive 24 h
3945
Pulizia del dato
3902
Analisi preliminare
2500

COSTRUZIONE DATASET

ID	time [h]	PaO2 [mmHg]	...	Ventilazione
IT999-1	0	84	...	IMV
IT999-1	1		...	IMV
IT999-1	2	78	...	IMV
IT999-1	3		...	IMV
IT999-1	4	82	...	IMV
IT999-1	5	80	...	IMV
...	...	...	...	...
IT999-1	22	93	...	NIV
IT999-1	23		...	NIV

PaO2 [mmHg]					
ID	time [h]	Min	Max	Mean	Median
IT999-1	[0, 23]	78	93	84	82
IT999-1	[24, 47]	81	92	86	86
IT999-1	[48, 71]	...	...	...	...

Ventilazione				
ID	time [h]	First	Last	Max
IT999-1	[0, 23]	IMV	NIV	IMV
IT999-1	[24, 47]	NIV	NIV	NIV
IT999-1	[48, 71]	...	...	...

VARIABILI

Estrazione diretta da MargheritaTre					
Base		**Cardiovascolari**	**Respiratorie**		
Sesso	Altezza	Pressione Sistolica	PFRatio	PEEP	FiO2
Peso	Eta	Pressione Diastolica	SaO2	Pressione di Picco	Pressione di Plateau
			Tidal Volume	Tipo di respirazione	Device ventilatiorio

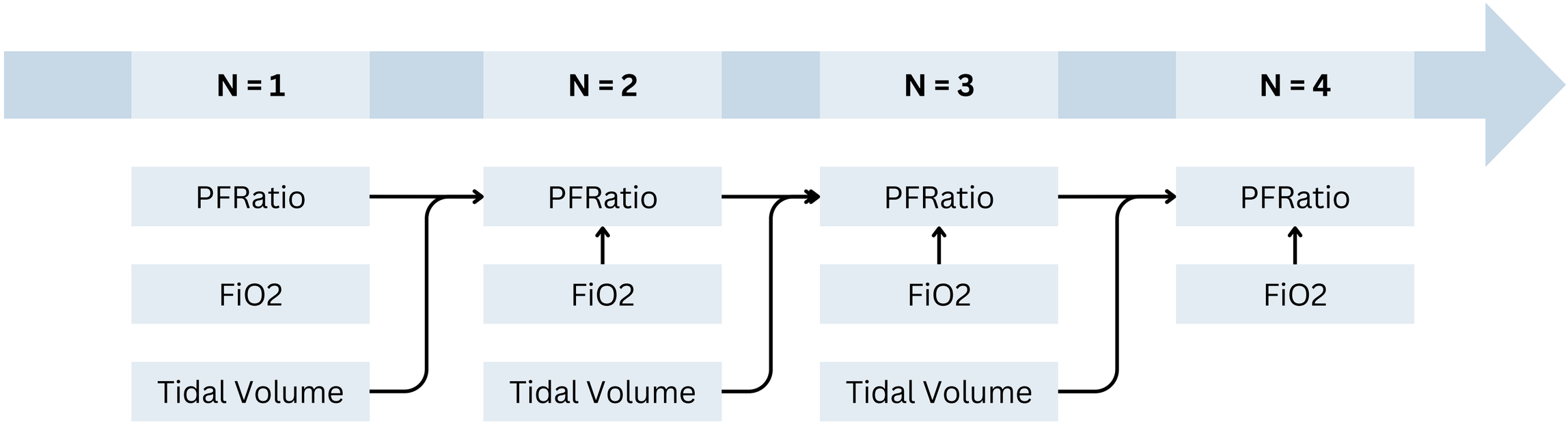
Derivate					
Base		**Respiratorie**			
Predicted Body Weight	BMI	Driving Pressure	Ventilazione	**Tidal Volume ml pro Kg** (PBW)	Compliance

MODELLI

Un modello per variabile

Ogni variabile al giorno *N* può dipendere da

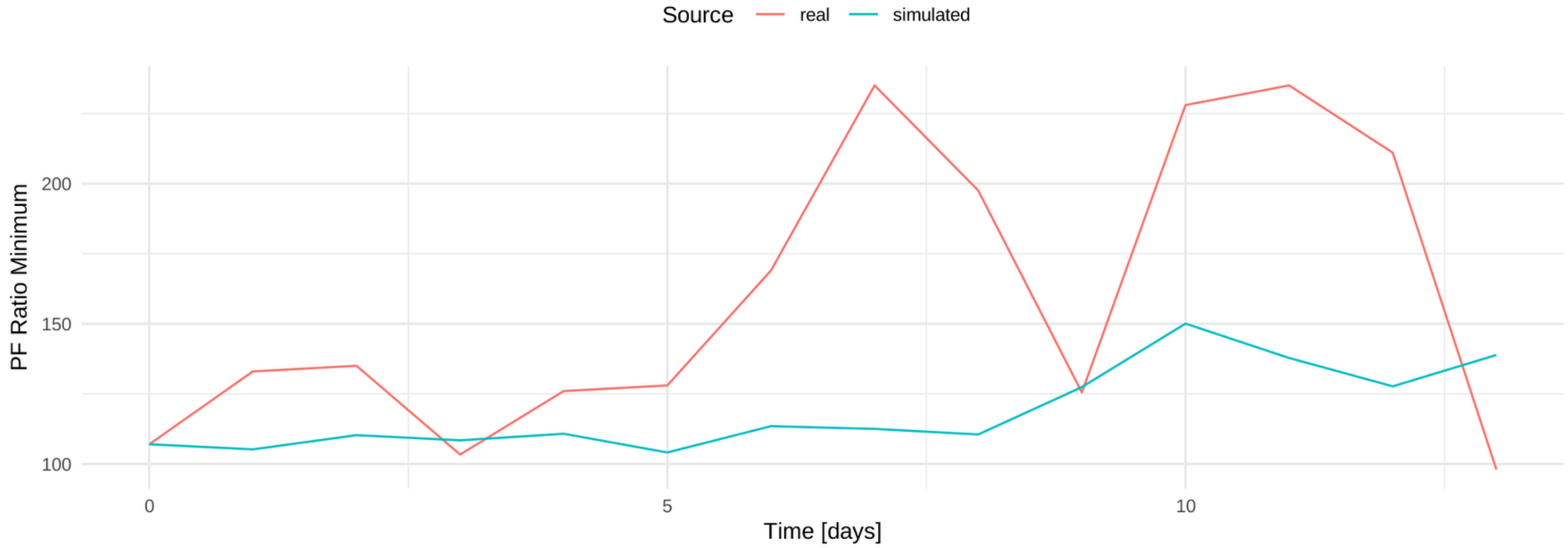
- altre variabili al giorno *N*
- la sua stessa *storia* (i valori che essa stessa assume nei giorni precedenti al giorno *N)*
- la *storia* delle altre variabili



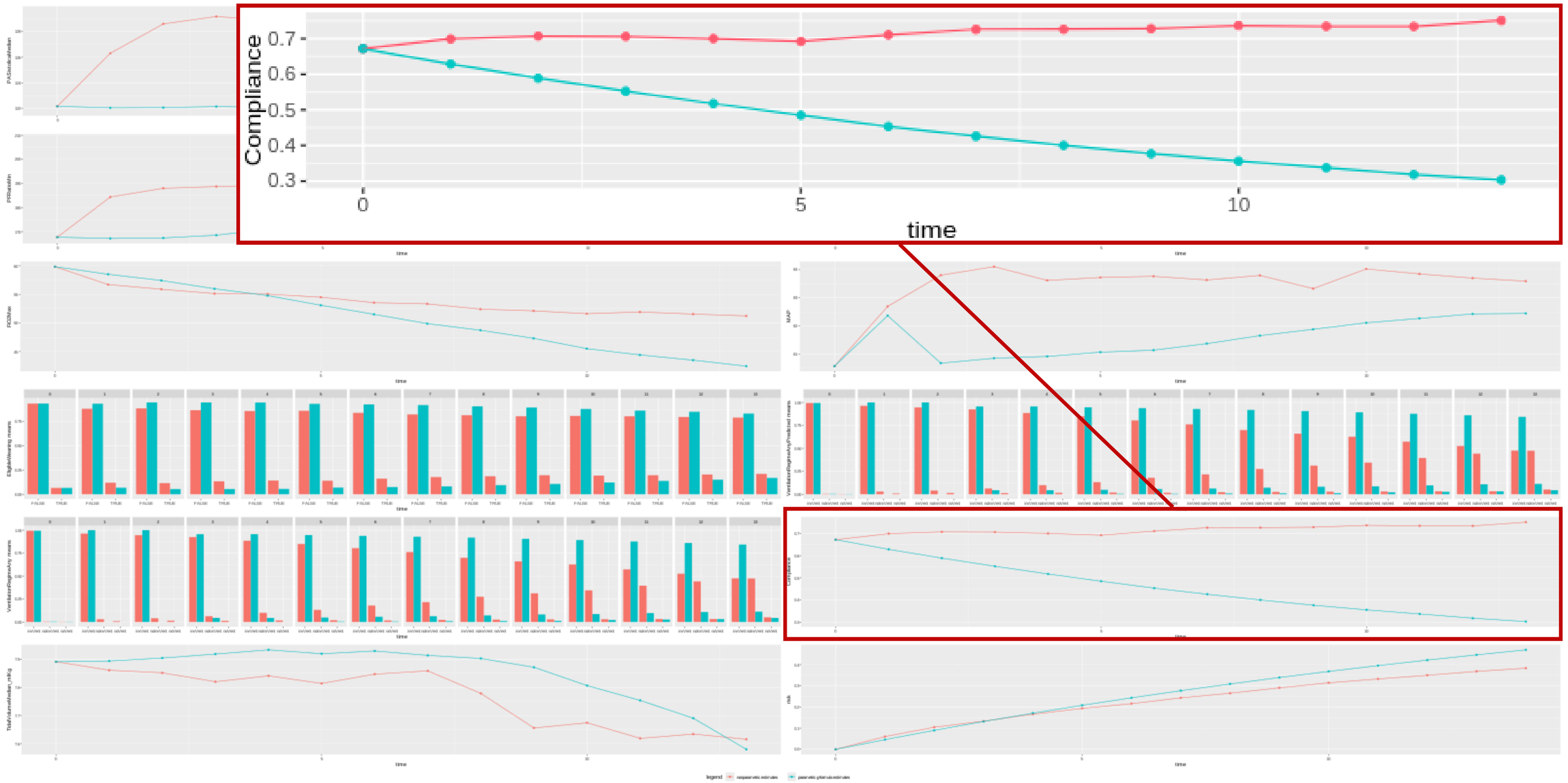
SIMULAZIONE “NATURAL COURSE”

A partire dalle variabili al giorno 1, vengono simulate tutte le variabili fino al giorno N = 14

PFRatio (N) ~ PFRatio (N-1) + PFRatio (N-2) + PFRatio (N-3) +
Ventilatione (N) + Ventilazione (N - 1) +
TidalVolume_mlKg (N-1) + FiO2 (N)



SIMULAZIONE “NATURAL COURSE”

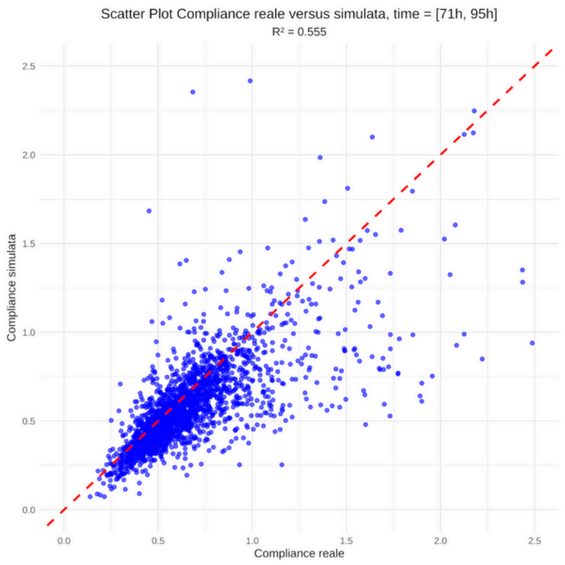


SIMULAZIONE “NATURAL COURSE”

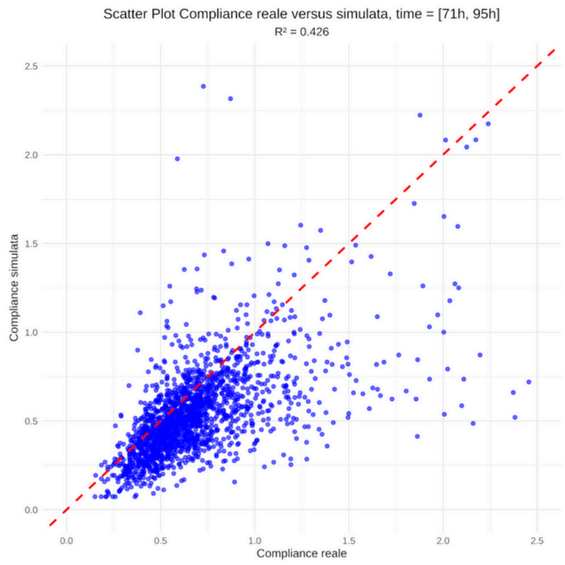
Modello Compliance (primo test)

Compliance (N) ~ Compliance (N-1) + Compliance (N-2) + Compliance (N-3)

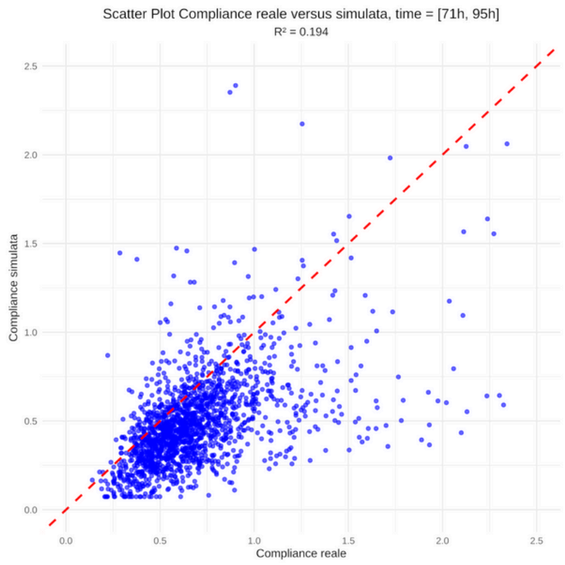
Giorno 2



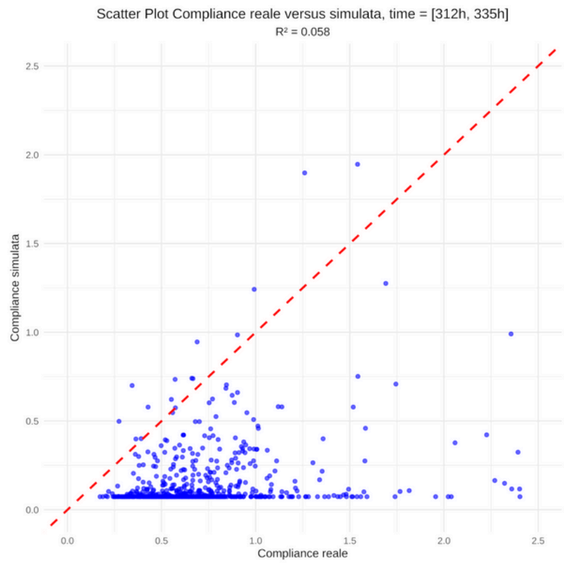
Giorno 3



Giorno 4



Giorno 14



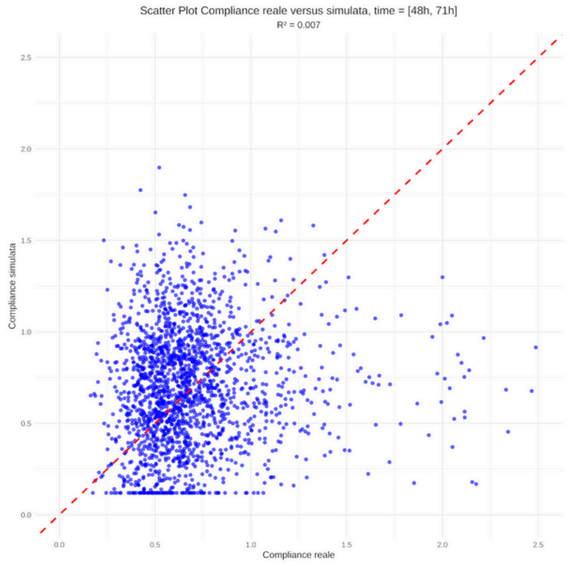
SIMULAZIONE “NATURAL COURSE”

Modello Compliance (ultimo test)

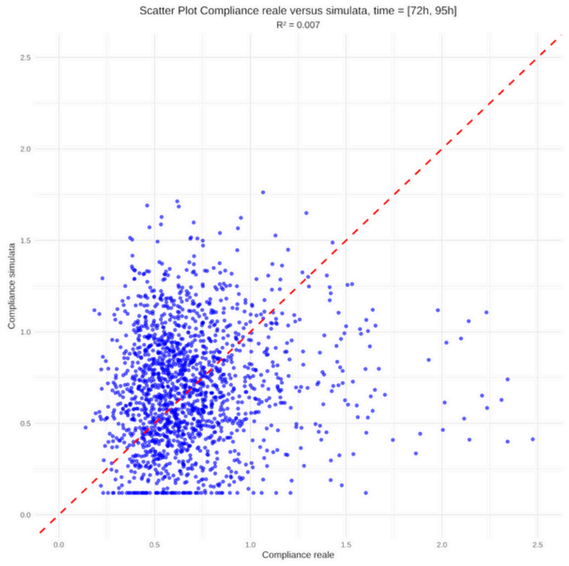
Compliance (N) ~ PEEP (N) + FiO2 (N) + SaO2 (N) + PSistolica (N) +
PEEP (N-1) + FiO2Max (N-1) + SaO2 (N-1) + PASistolica (N-1) + PBW + BMI

Giorno 2

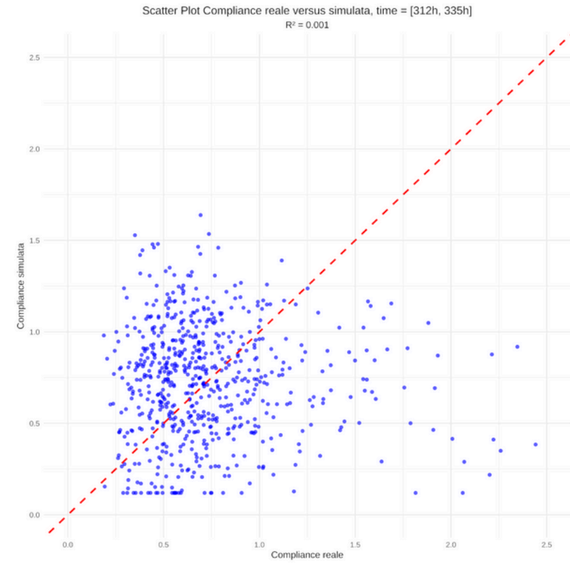
Giorno 3



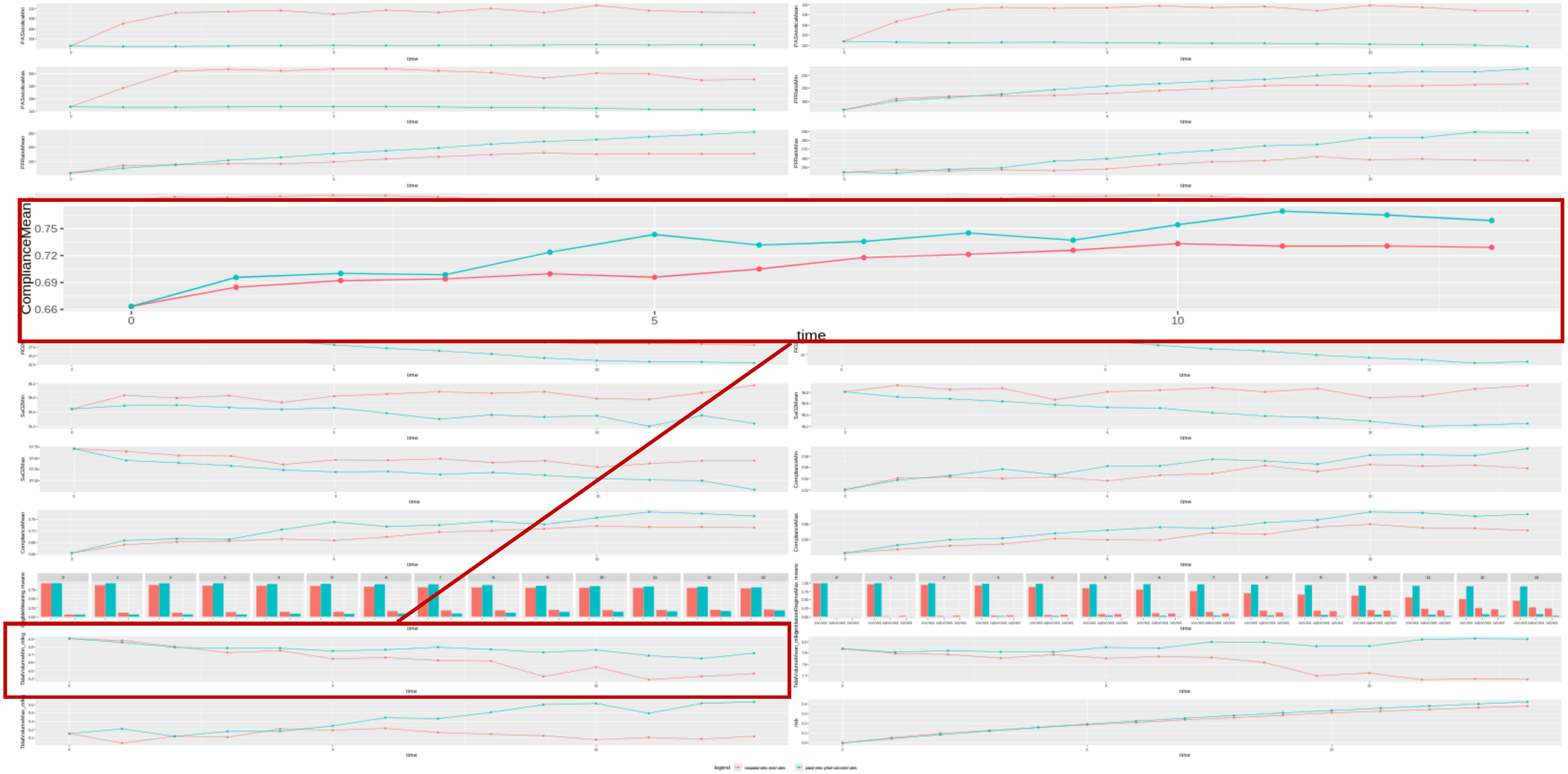
Giorno 4



Giorno 14



SIMULAZIONE “NATURAL COURSE”



INTERVENTI

Definizione “intervento”

- Seleziono una variabile su cui il clinico può agire nella realtà (**Tidal Volume ml pro kg**)
- Definisco in che modo agire sulla variabile

INTERVENTI

Definizione “intervento”

- Seleziono una variabile su cui il clinico può agire nella realtà (**Tidal Volume ml pro kg**)
- Definisco in che modo agire sulla variabile

“**Low TV”**

- Tidal Volume (N) simulato secondo lo stesso modello usato per il Natural Course
  - Se Tidal Volume (N) <= 6 -> Tidal Volume (N) = 6
  - Se 6 < Tidal Volume (N) < 8 -> non modifico il valore simulato
  - Se Tidal Volume (N) >= 8 -> Tidal Volume (N) = 8

INTERVENTI

Definizione “intervento”

- Seleziono una variabile su cui il clinico può agire nella realtà (**Tidal Volume ml pro kg**)
- Definisco in che modo agire sulla variabile

“**Low TV”**

- Tidal Volume (N) simulato secondo lo stesso modello usato per il Natural Course
  - Se Tidal Volume (N) <= 6 -> Tidal Volume (N) = 6
  - Se 6 < Tidal Volume (N) < 8 -> non modifico il valore simulato
  - Se Tidal Volume (N) >= 8 -> Tidal Volume (N) = 8

“**High TV”**

- Tidal Volume (N) simulato secondo lo stesso modello usato per il Natural Course
  - Se Tidal Volume (N) <= 8 -> Tidal Volume (N) = 8
  - Se 8 < Tidal Volume (N) < 12 -> non modifico il valore simulato
  - Se Tidal Volume (N) >= 12 -> Tidal Volume (N) = 12

INTERVENTI

High TV

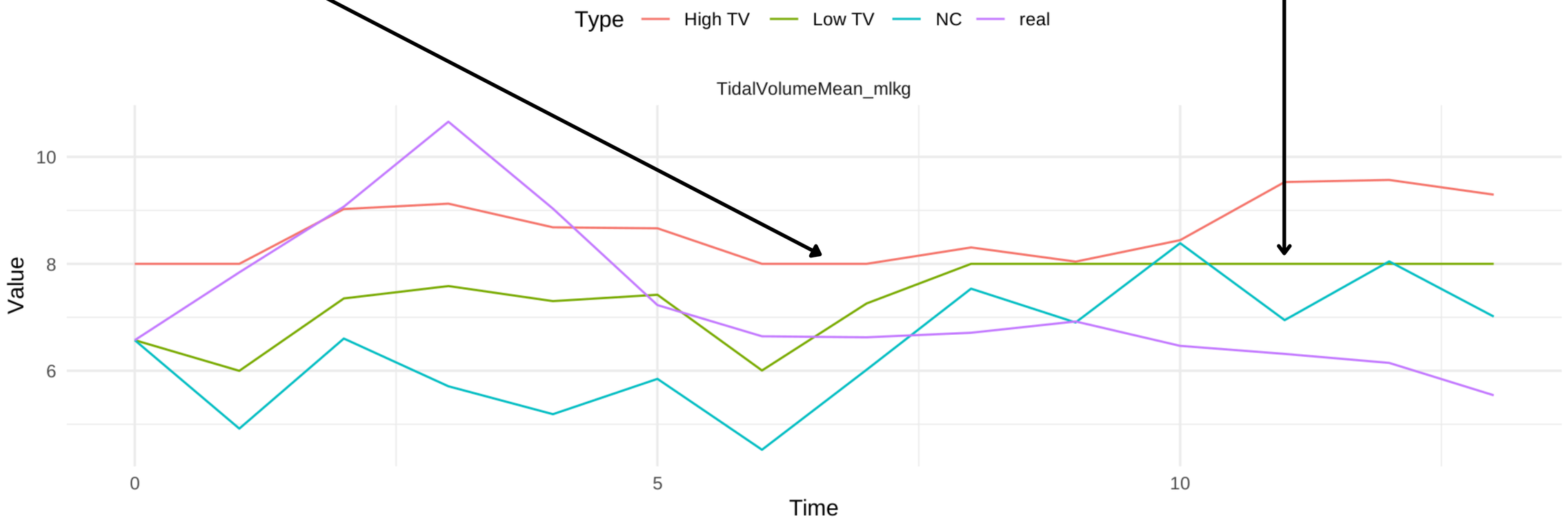
TV simulato <= 8

-> intervento: TV = 8 ml/kg

Low TV

TV simulato >= 8

-> intervento: TV = 8 ml/kg



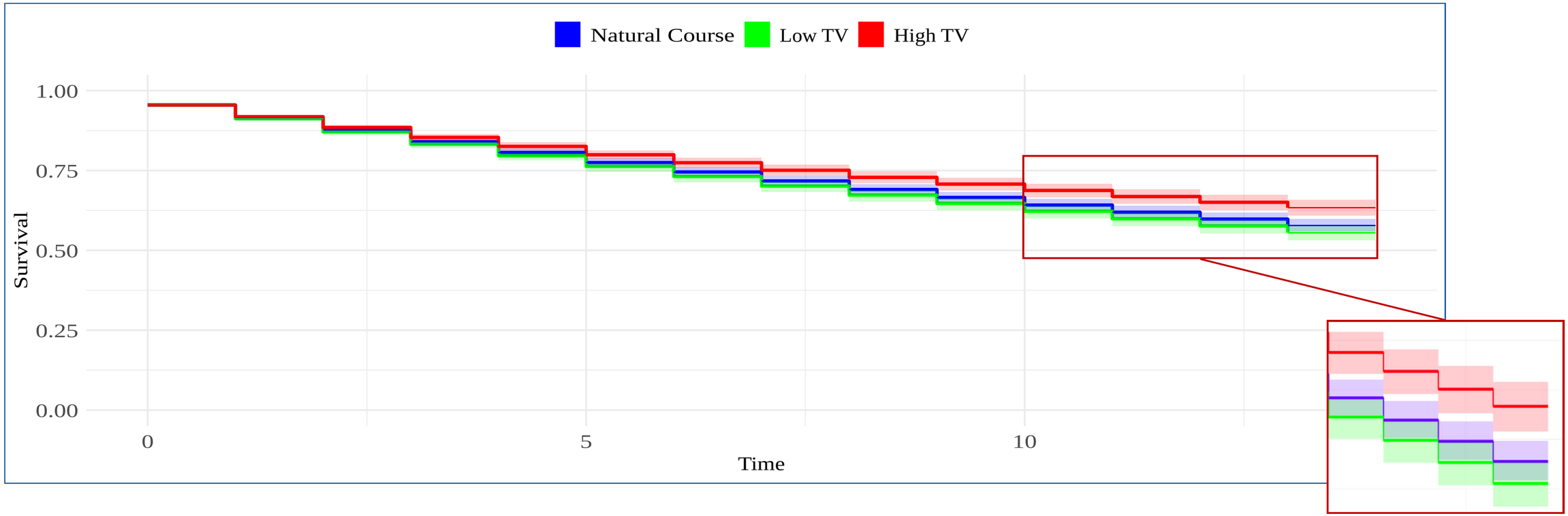
RISULTATI PRELIMINARI

Modello Mortalità (ultimo test)

Compliance (N) ~ Sesso + Eta + BMI +
Ventilazione (N) + TidalVolume (N) + PFRatio (N)

Intervalli di confiidenza al 95%

NBootstrap = 20



PROSPETTIVE FUTURE

Raffinare modello

Applicazione e confronto di nuove tecniche

Sviluppo di una piattaforma GiViTI per Emulated Target Trials

Collaborazioni internazionali

GRAZIE

RISULTATI PRELIMINARI

Modello Mortalità (ultimo test)

Compliance (N) ~ Sesso + Eta + BMI +
Ventilazione (N) + TidalVolume (N) + PFRatio (N)

time	Intervention	NP risk	g-form risk	Risk ratio	Intervened On (%)
13	0	0.379	0.422 (0.402, 0.441)	1	
13	LowTV		0.445 (0.423, 0.468)	1.052	99.71
13	HighTV		0.367 (0.342, 0.392)	0.868	96.94