

Year in Review

Clinical studies and future developments

J.G. van der Hoeven - NVIC 2023

Contents

- Mechanical ventilation and weaning
- Circulation, fluid therapy and eCPR
- All that is left.....

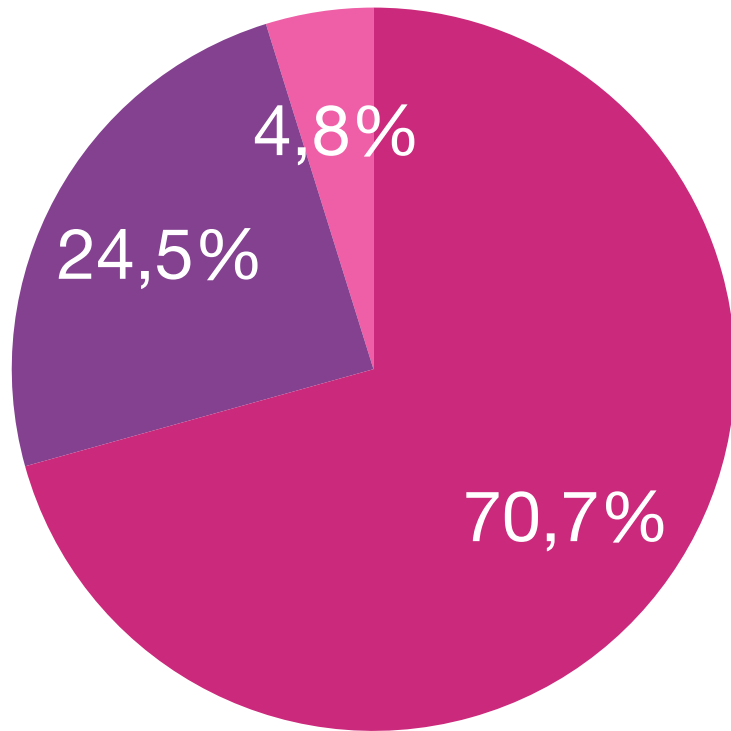
Dyspnea in mechanically ventilated patients

- Prospective cohort study in 10 centers investigating the prevalence and severity of dyspnea and its effect on ICU LOS and PTSD at D90
- Dyspnea investigated in patients intubated > 24 hrs with VAS (1 - 10) as soon as they were able to communicate, following day and prior to SBT
- PTSD defined as Impact of Event Scale-Revised score > 10
- Comparison of patients with and without dyspnea

Dyspnea in mechanically ventilated patients

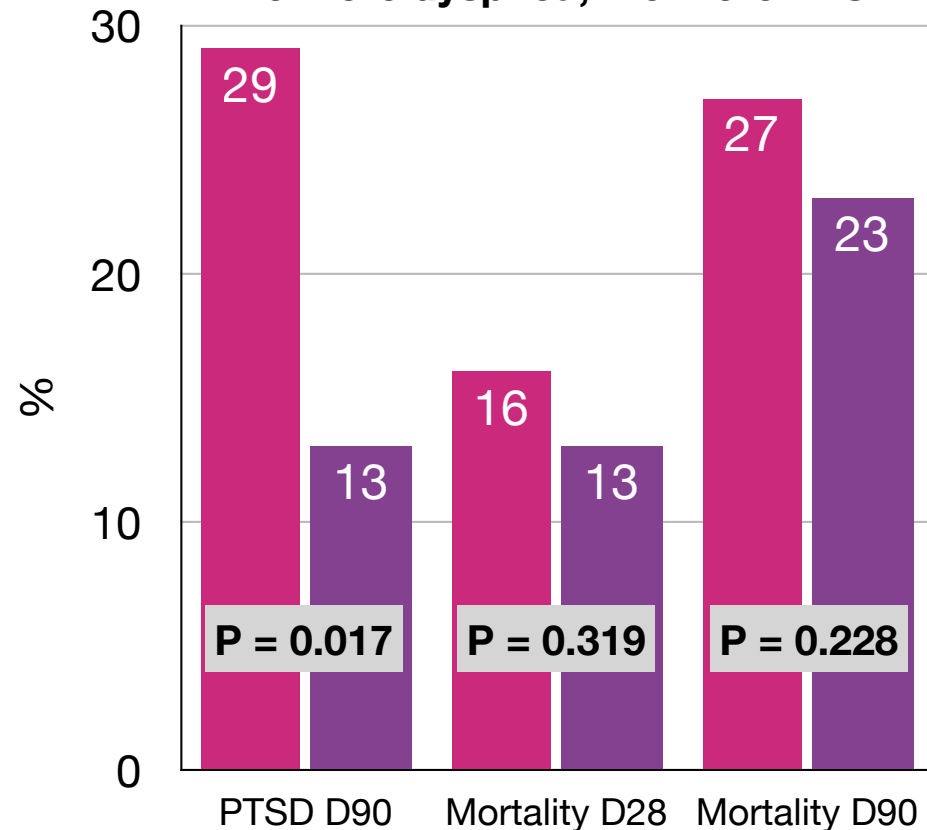
A total of 612 patients included

- Air hunger
- No response
- Excessive effort



208/612 patients with dyspnea (34%)

The more dyspnea, the more PTSD

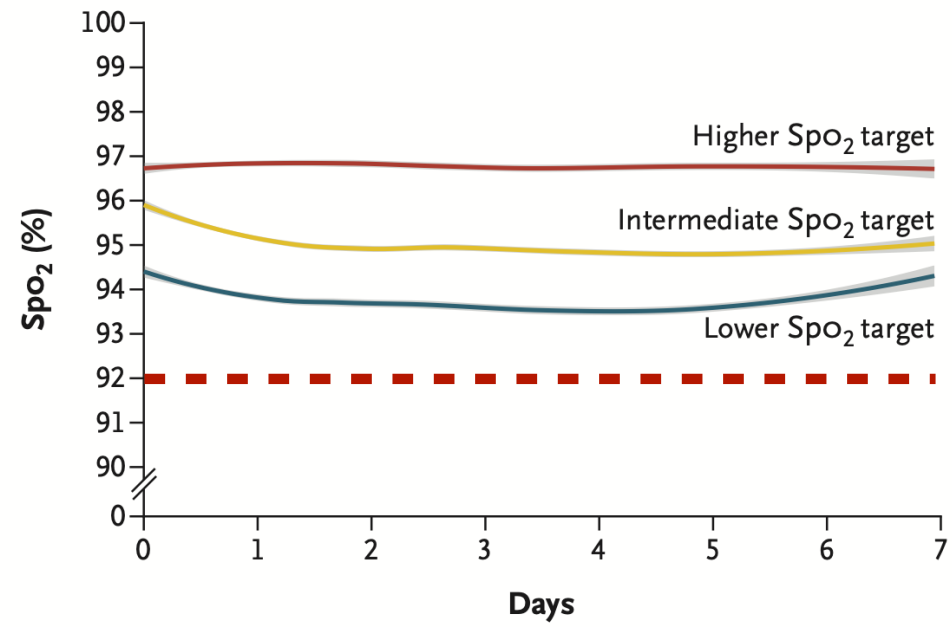


No differences in ICU LOS, hospital LOS, VFD's

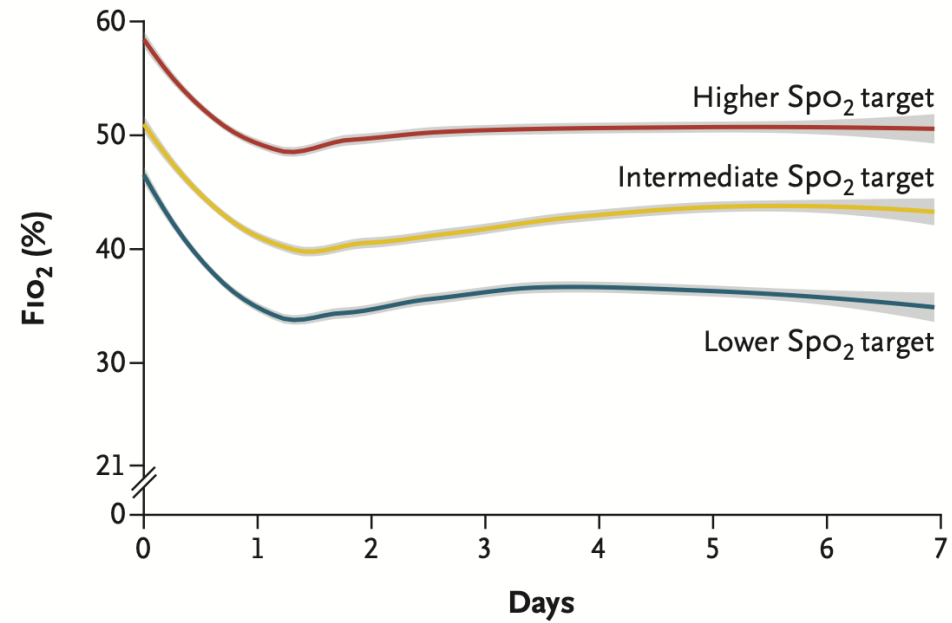
Oxygen saturation targets for critically ill patients on MV

- Cluster-randomized crossover trial in ED and medical ICU of academic hospital comparing SpO₂ targets of 88-92%, 92-96% and 96-100%
- Adult patients receiving mechanical ventilation
- 36 months with 18 clusters of 2 months of different SpO₂ targets
- Primary outcome: VFD's D28
- Secondary outcome: Mortality D28

A



B



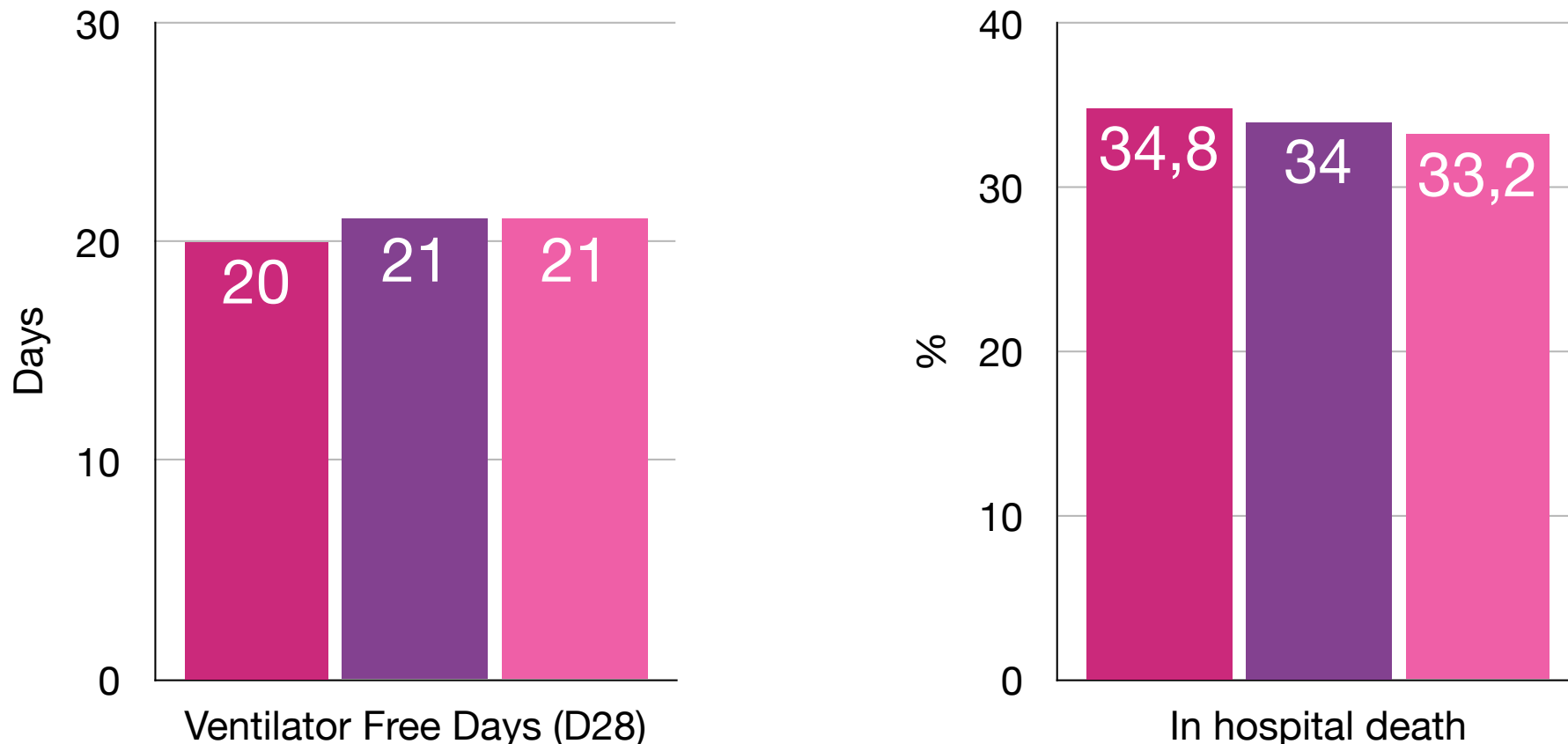
No. at Risk

Higher	874	599	411	302	233	175	138	110
Intermediate	859	597	415	320	251	193	159	134
Lower	808	532	360	245	192	149	117	92

Oxygen saturation targets for critically ill patients on MV

N = 2541

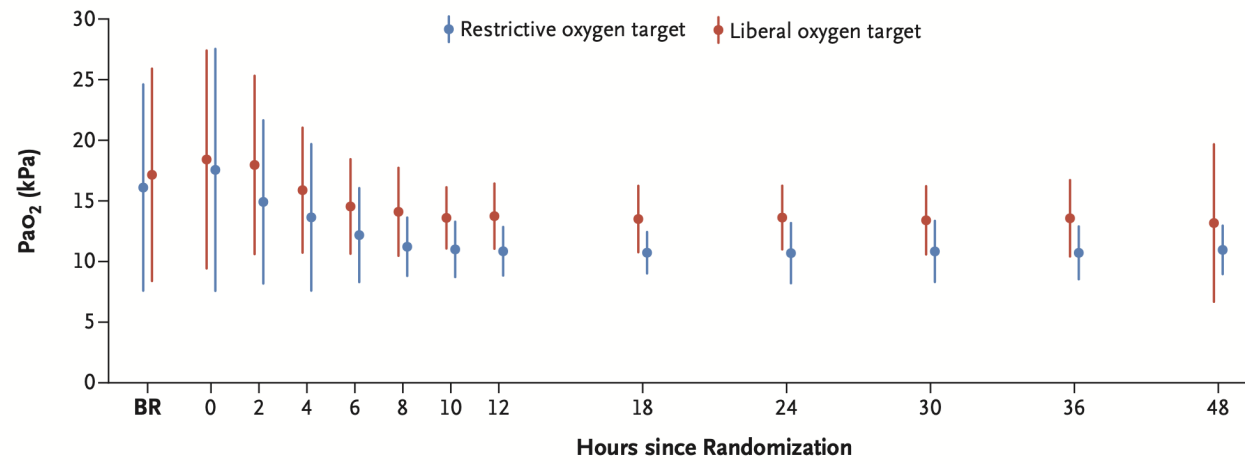
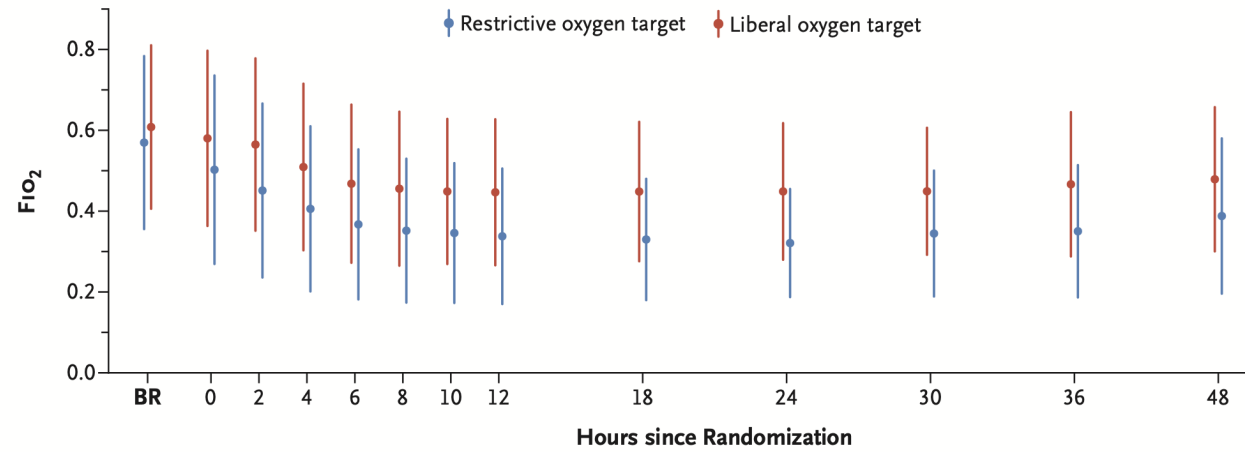
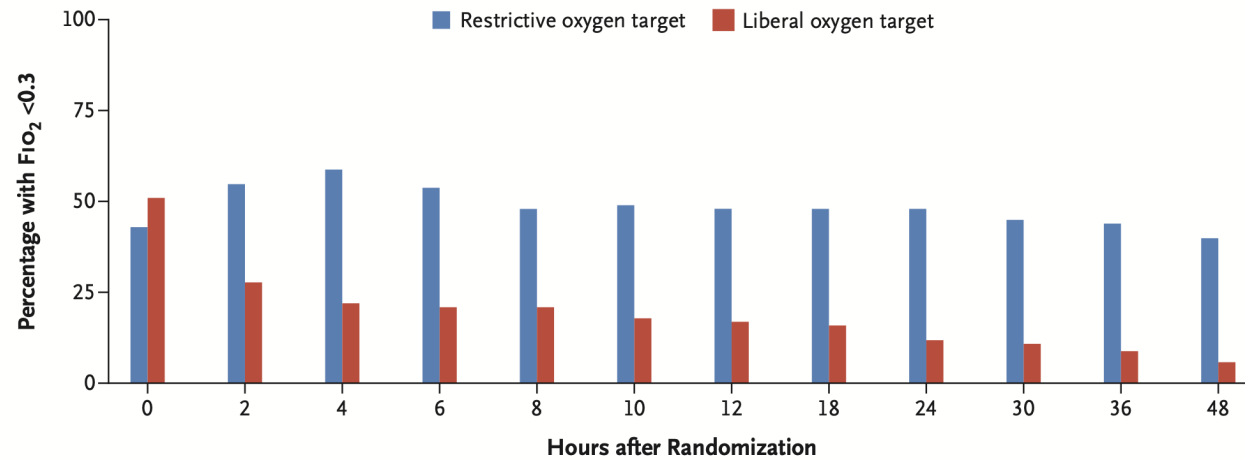
88 - 92% 92 - 96% 96 - 100%



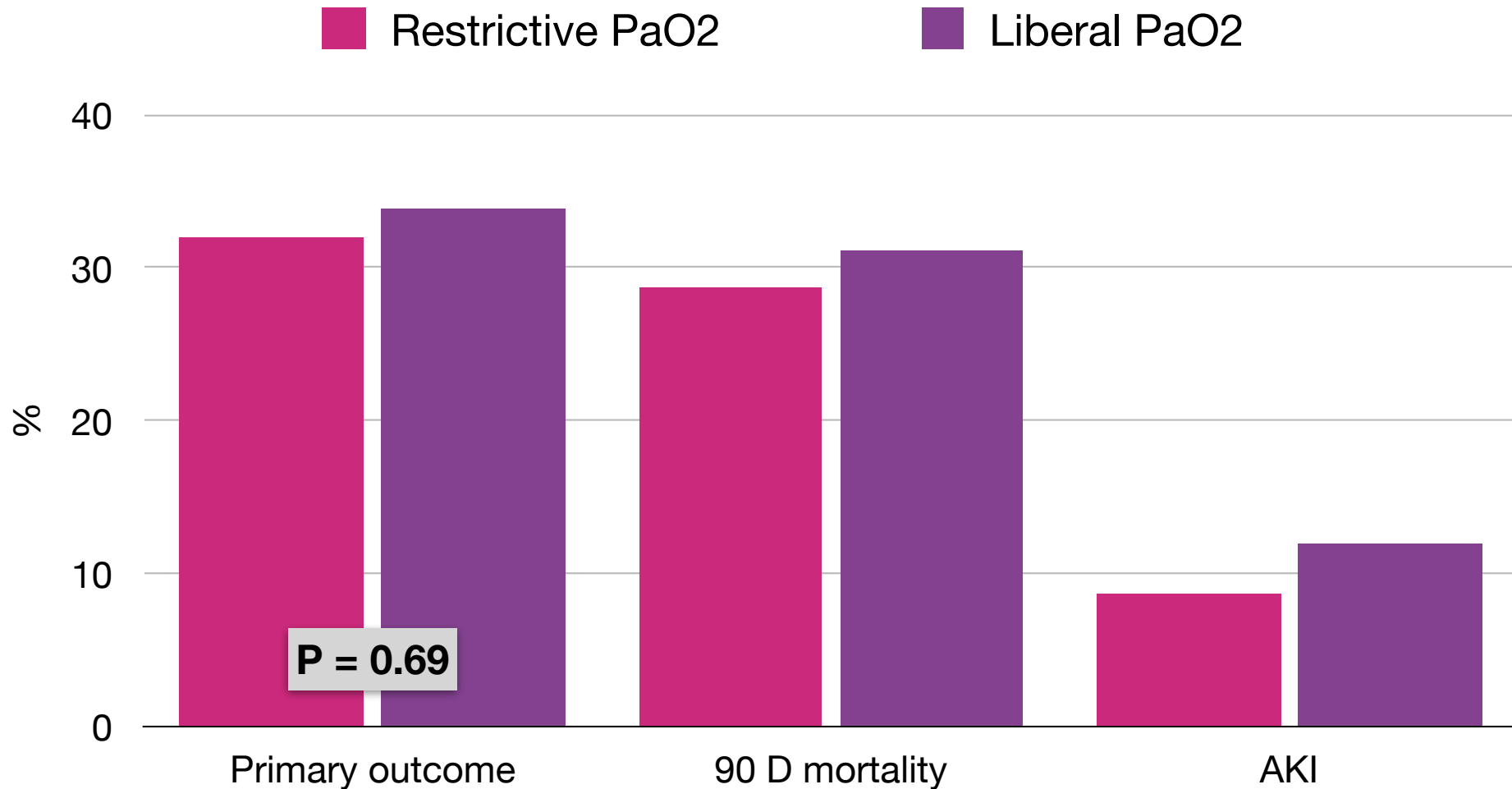
No differences in cardiac arrest, arrhythmia, myocardial infarction, stroke, pneumothorax

Oxygen targets in comatose survivors of OHCA

- RCT (2×2 factorial design) comparing restrictive PaO₂ (9-10 kPa) with liberal PaO₂ (13-14 kPa) in 789 adult comatose survivors after OHCA (unwitnessed asystole excluded) treated with TTM - both groups always SpO₂ > 92%
- Primary outcome: composite of death or discharge with CPC 3/4 within D90
- Secondary outcome: NSE levels at 48 hrs, death from any cause, Montreal Cognitive Assessment and Rankin scale assessment and CPC at 3 months

A Partial Pressure of Arterial Oxygen**B Fraction of Inspired Oxygen****C Percentage of Patients with Fraction of Inspired Oxygen <0.3**

Oxygen targets in comatose survivors of OHCA

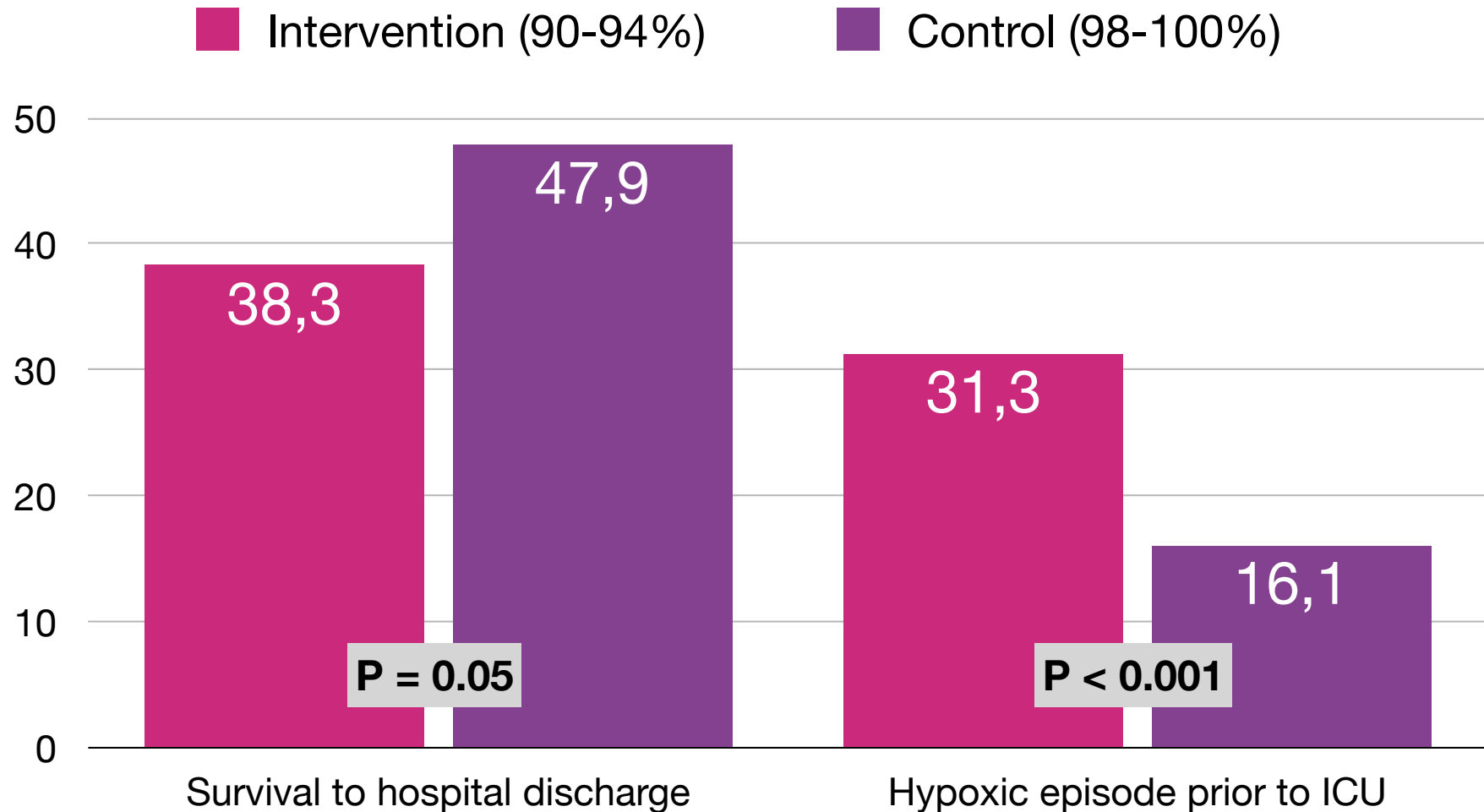


No differences in CPC, mRS or MCA score at 3 months, NSE or SAE's

Lower vs higher SpO₂ in patients with OHCA

- RCT in comatose patients successfully resuscitated from OHCA comparing a titrated prehospital SpO₂ of 90 - 94% with an SpO₂ of 98 - 100% until arrival in the ICU
- Primary outcome: survival until hospital discharge
- Multiple (9) secondary outcomes including hypoxic episodes, SAE's, rearrest etc etc
- Trial stopped early due to COVID-19 after 428 patients (planned 1416) of whom 425 included in analysis

Lower vs higher SpO₂ in patients with OHCA

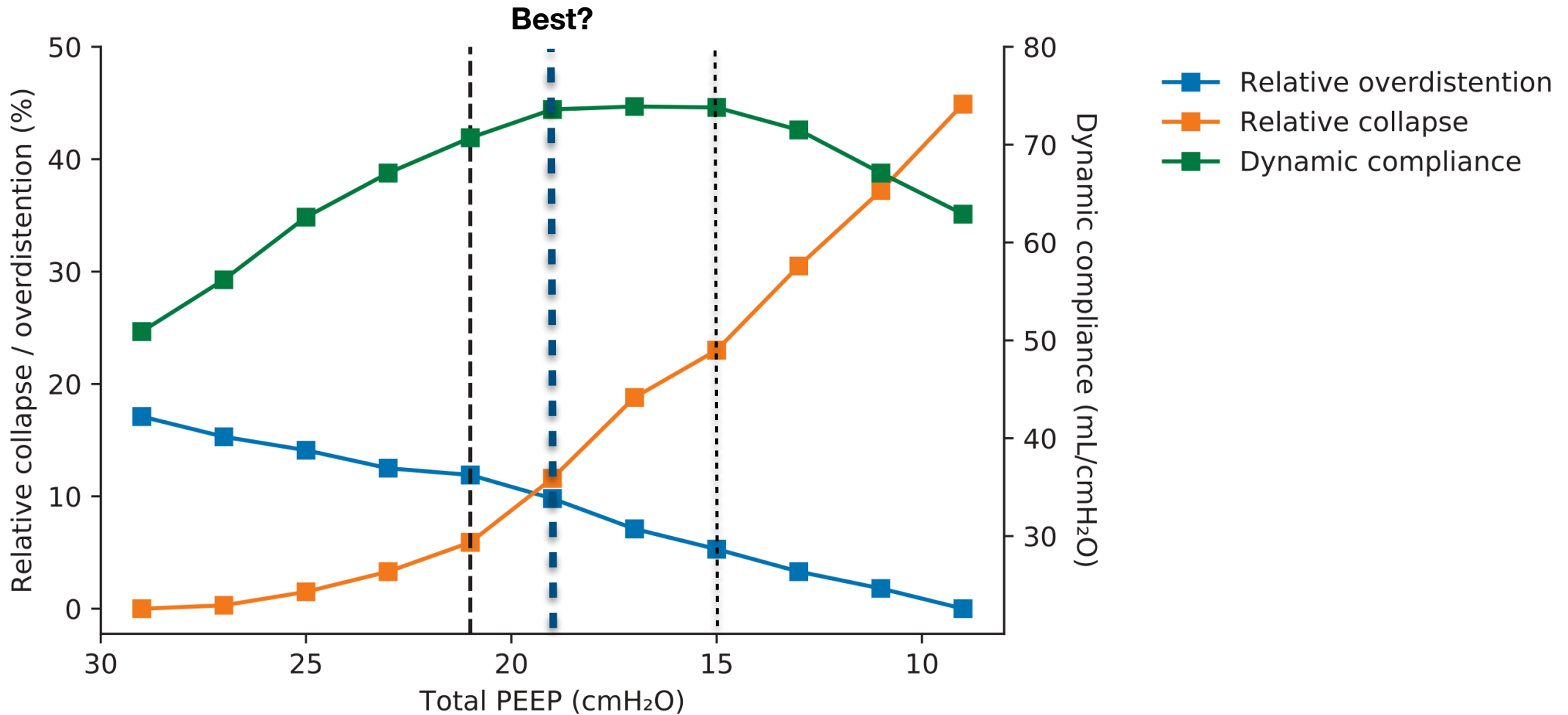


No differences in rearrest, peak troponin, ICU and hospital LOS, CPC score, discharge destination

For the future

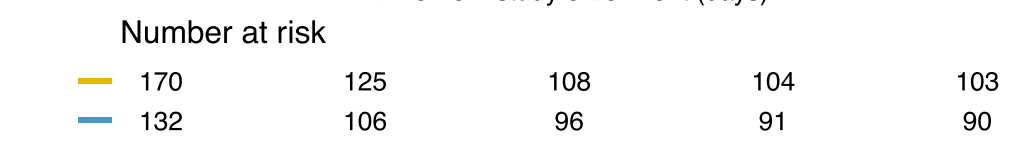
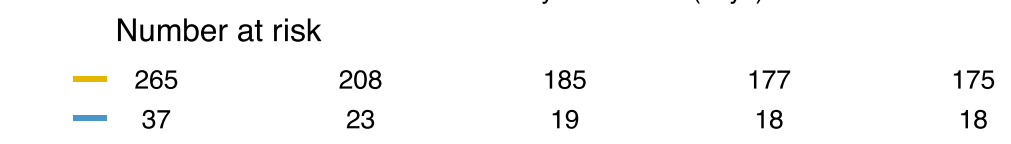
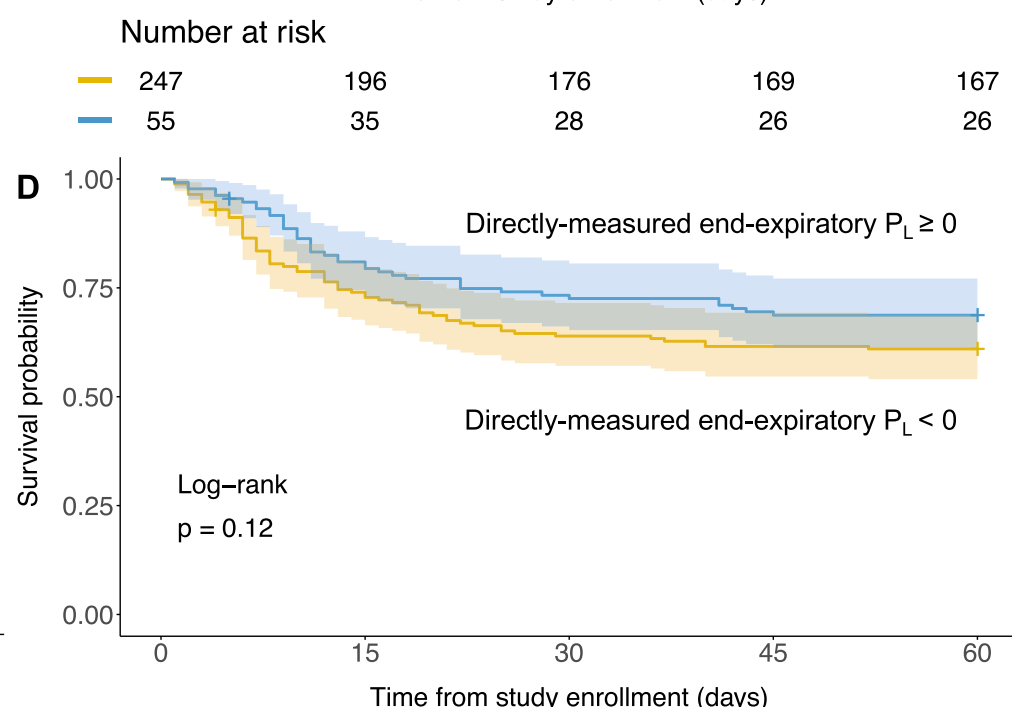
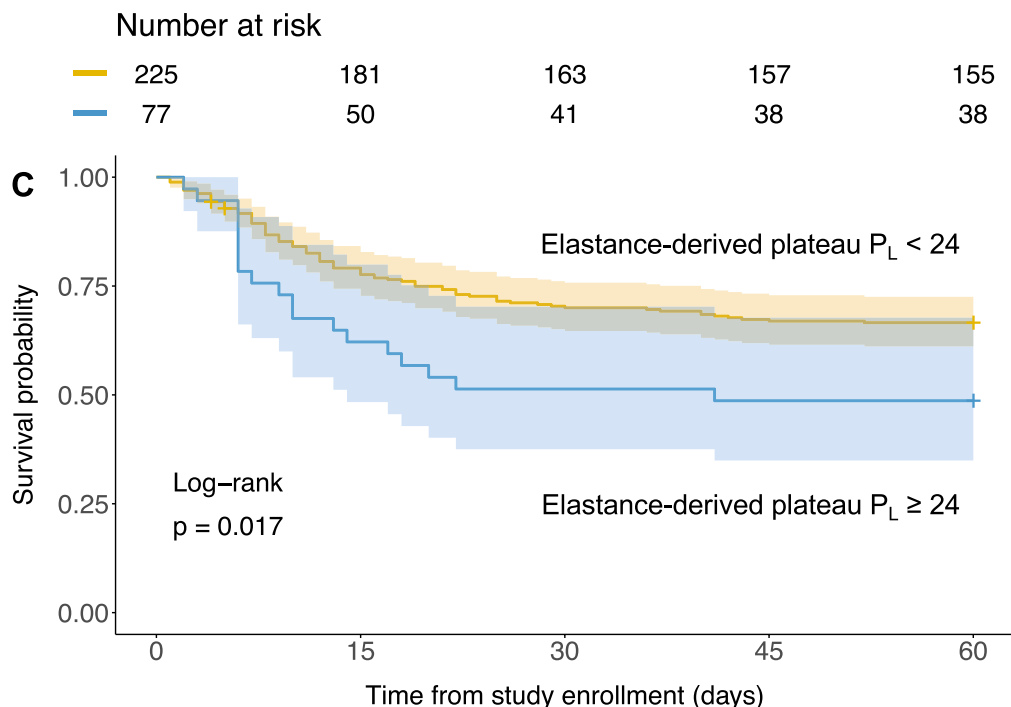
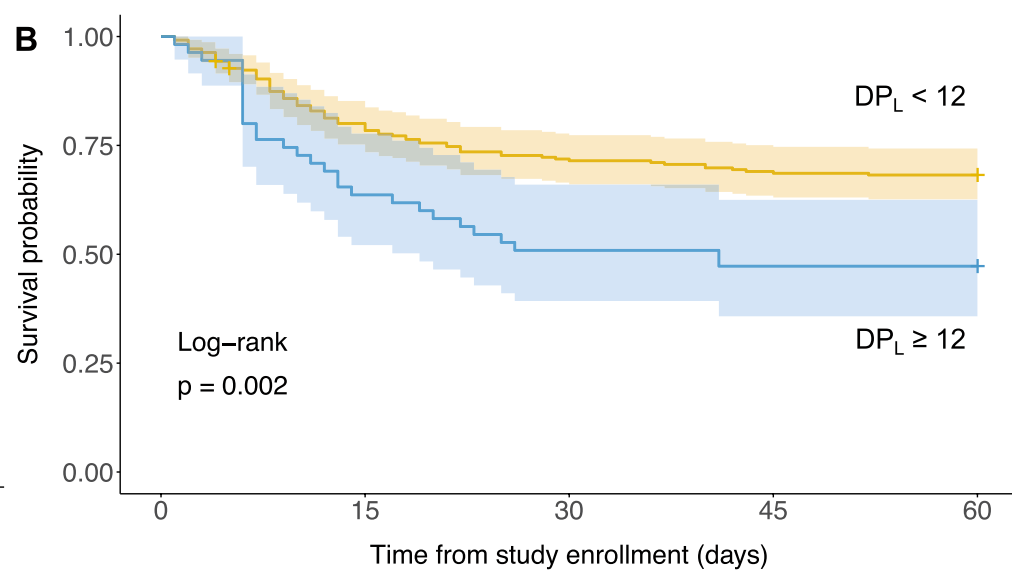
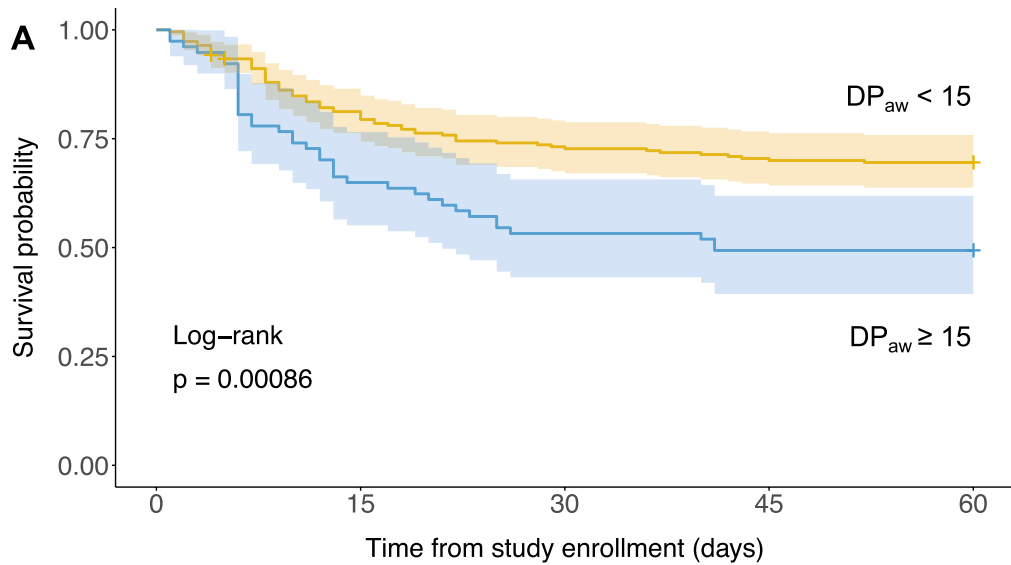
- No evidence that normal (or even slightly increased) SaO₂ or PaO₂ levels have a negative impact on outcome
- Extreme hyperoxia (PaO₂ > 25 kPa) should still be avoided but permissive hypoxia is dangerous for certain patient groups (especially if combined with permissive hypotension, low hemoglobin levels and fluid restriction)
- Dyspnea sensation may have an important effect on longterm outcome and effective measures for prevention should be investigated

Hyperinflation or recruitment-derecruitment most damaging?



No major trials available but

Observational study in 385 patients linking physiology to outcome



For the future

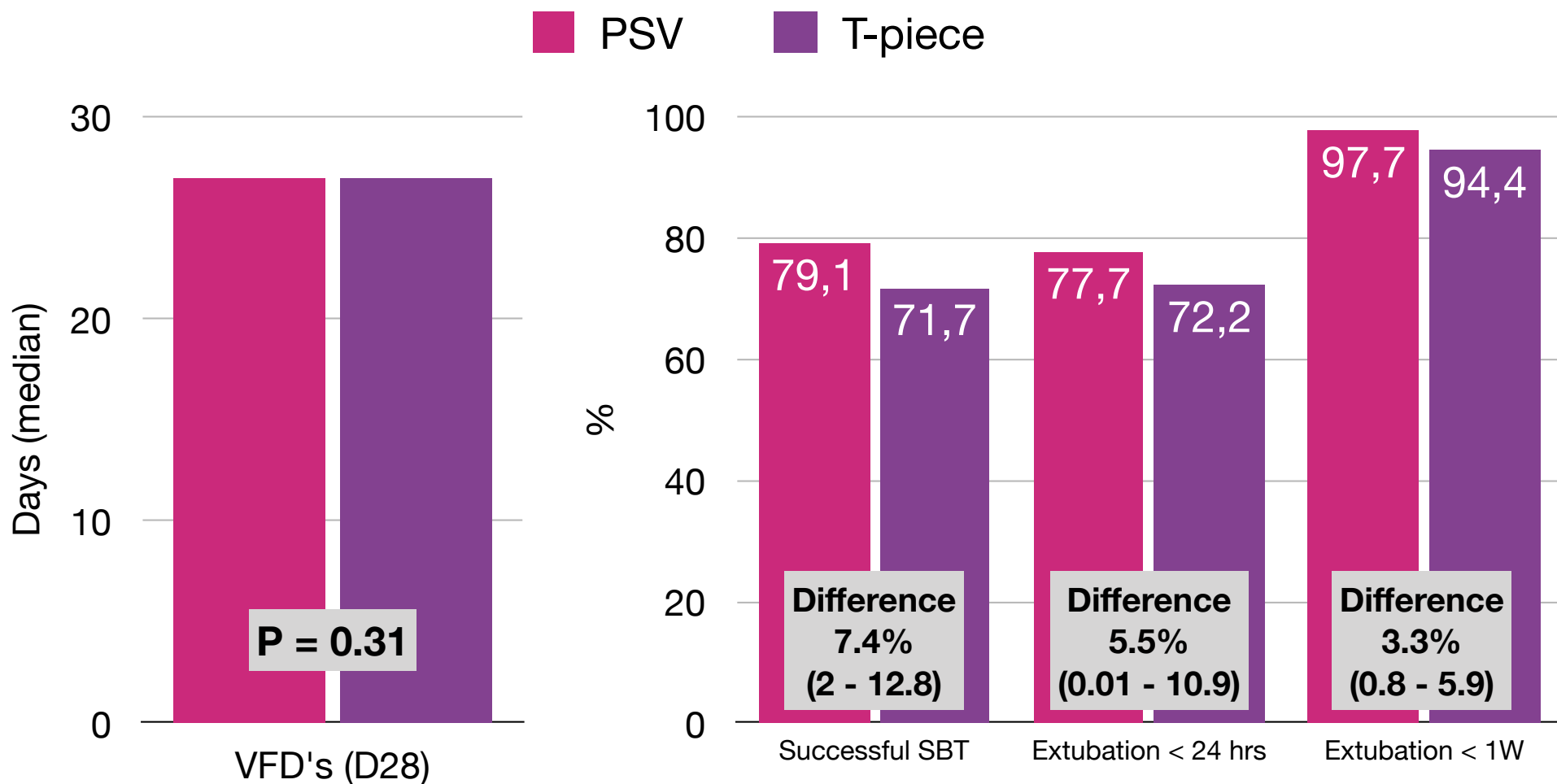
- To determine if DP is a better target than Tv or Pplat and determine the individual cut-off level
- Determine if hyperinflation or recruitment-derecruitment is the most damaging in an individual patient (online exhaled air measurement of DAMP's and inflammatory parameters)
- Determine in which patients with ARDS MV should be avoided at all (immediate rescue ECLS)

PSV or T-piece trial in patients with high risk of extubation failure

- MC (N=31) RCT comparing PSV (8 cm H₂O, FiO₂ ≤ 40%, no PEEP) or T-piece trial (O₂ 6L/min) for 1 hr in patients with high risk of extubation failure (age > 65 or any chronic respiratory or cardiac disease) - TBI and NMD patients excluded
- After extubation NIV or HFNO for 48 hrs encouraged
- Primary outcome: VFD's at D28
- Secondary outcomes: VFD's at D28 including NIV, successful SBT, level of weaning difficulty, reintubation < 7 D, ICU mortality and mortality at D28 and D90

PSV or T-piece trial in patients with high risk of extubation failure

N = 969 (similar baseline characteristics)



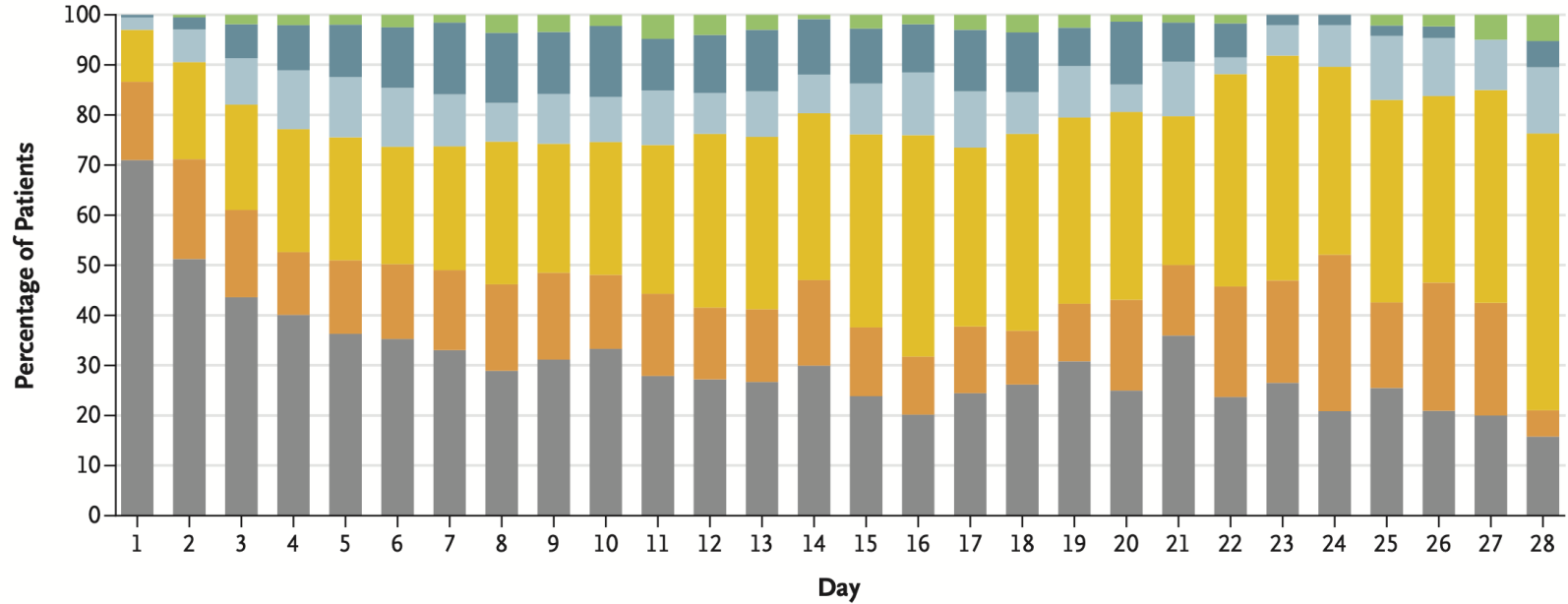
No differences in reintubation rate at D7 or mortality

Early mobilization during MV in the ICU

- MC RCT in mechanically ventilated adult patients (N=750) comparing increased early mobilization with standard of care (primary brain and spinal injury excluded) from up to 28 D
- Increased early mobilization defined as highest possible level deemed to be safe for as long as possible
- Primary outcome: number of days alive and out of hospital at D 180
- Secondary outcomes: Mortality D 180, VFD's D28, PROM's, adverse events

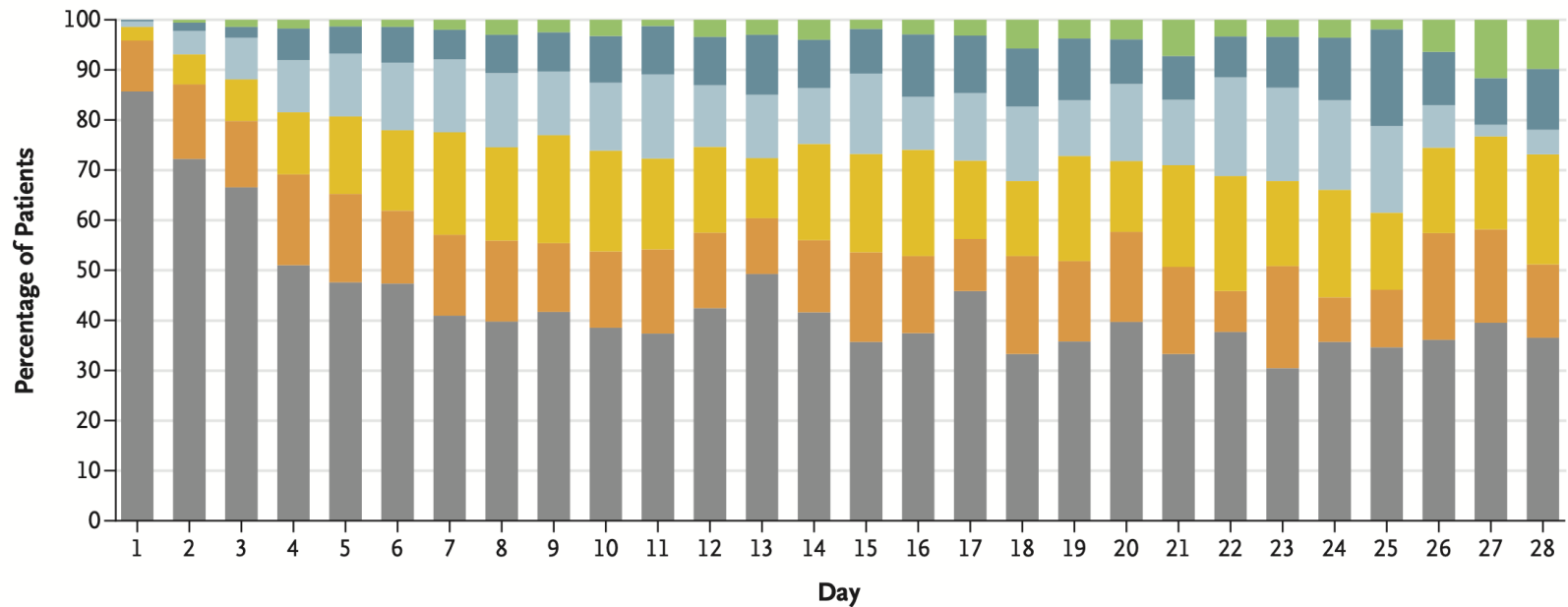
ICU Mobility Scale: 0 (nothing or passive) 1-2 (in-bed or in-chair exercises) 3-4 (active sitting or standing) 5-6 (transfer or marching in place) 7-8 (assisted walking) 9-10 (independent walking)

A Early Mobilization



No. of Patients 365 371 367 342 306 281 251 221 202 177 165 147 131 117 109 104 98 84 78 72 64 59 49 48 47 43 40 38

B Usual Care



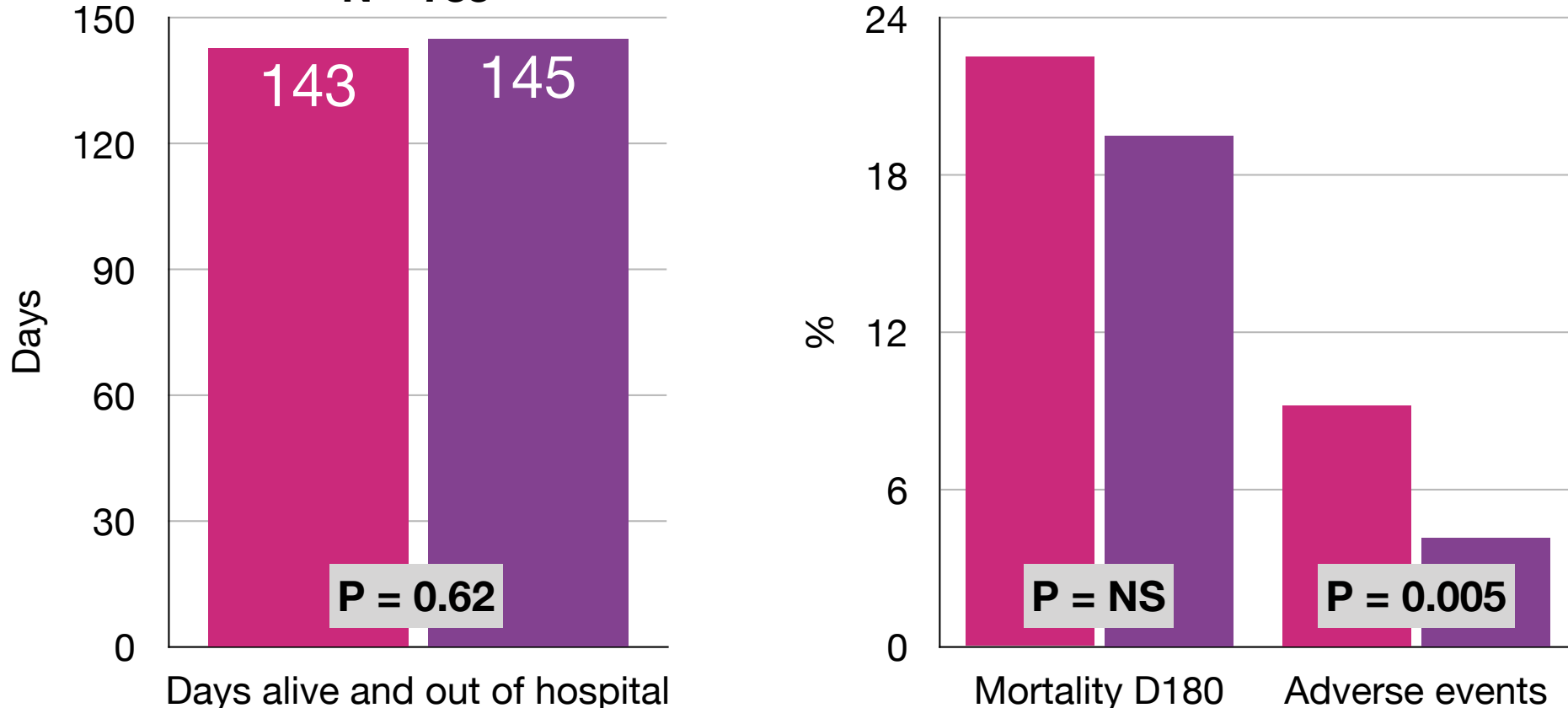
No. of Patients 363 364 362 347 311 281 254 236 204 184 166 146 134 125 112 104 96 87 81 78 69 61 59 56 52 47 43 41

Early mobilization during MV in the ICU

Mean daily duration of active mobilization 20.8 ± 14.6 vs 8.8 ± 9.0 min

■ Early mobilization ■ Usual-care

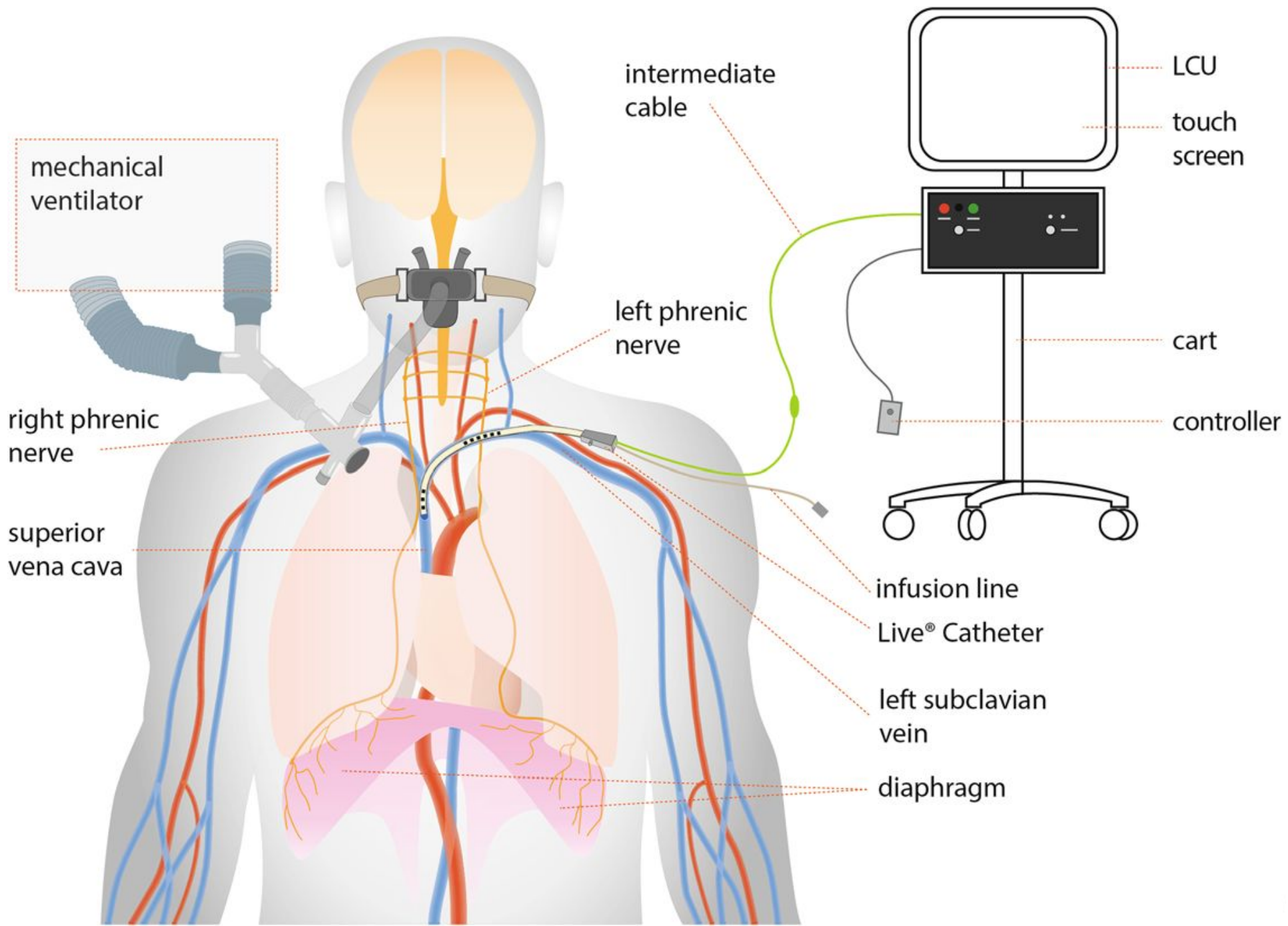
N = 733



No differences in QoL, activities daily living, disability, cognitive function, psychological function

Temporary trans venous phrenic nerve stimulation in difficult weaning

- MC, open-label RCT in adults investigating transvenous diaphragm stimulation in difficult to wean patients (MV \geq 4 D having failed \geq 2 weaning attempts) - standard weaning protocol - 120 stimulations/day for 30 D
- Primary outcome: proportion of successfully weaned patients
- Secondary outcomes: duration MV, 30-D survival, MIP, diaphragm thickening fraction, adverse effects and stimulation related pain
- In 14 out of 57 patients TV pacing was not possible

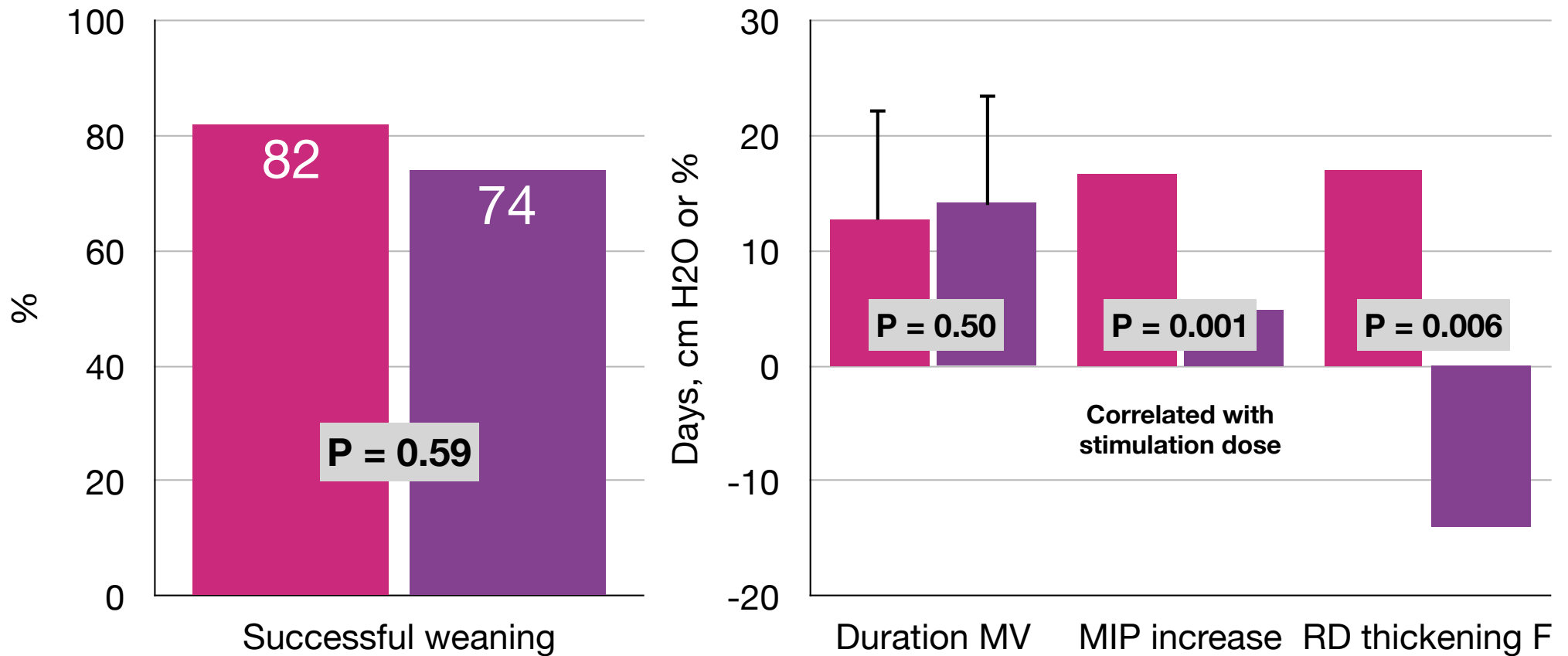


Lungpacer Medical

Temporary trans venous phrenic nerve stimulation in difficult weaning

Prior period of MV before inclusion approximately 4 weeks

■ TV stimulation (N=43) ■ Control (N=55)



No differences in adverse events - no pain in TV stimulation group

For the future

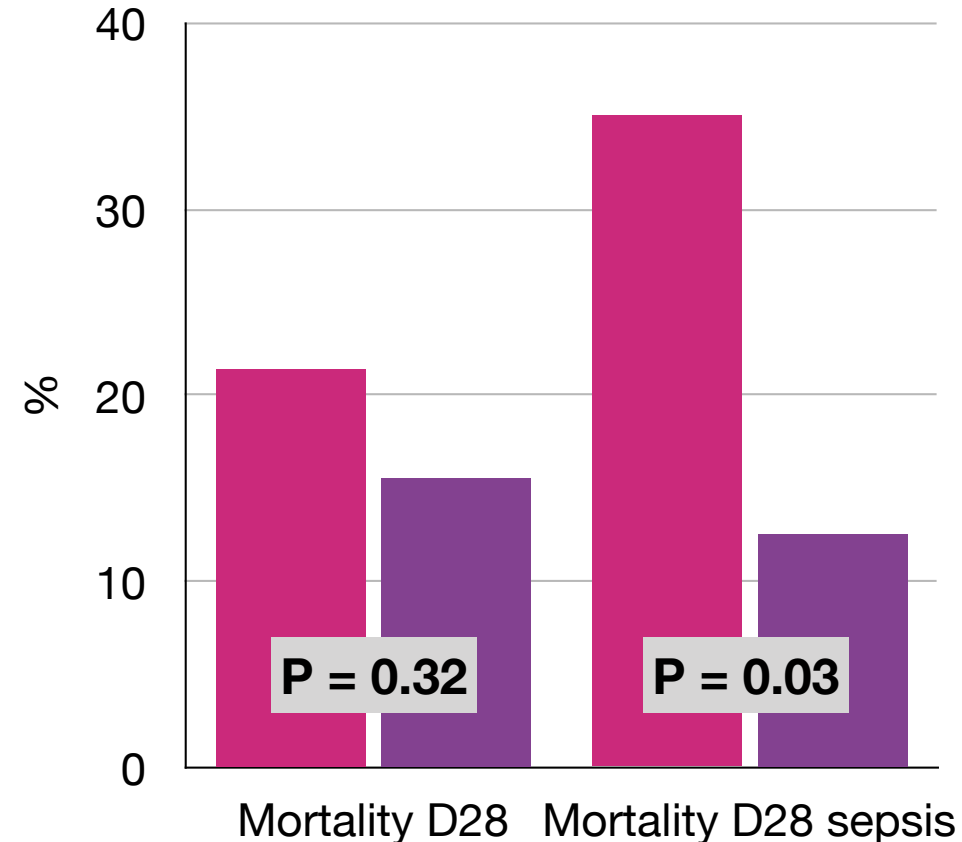
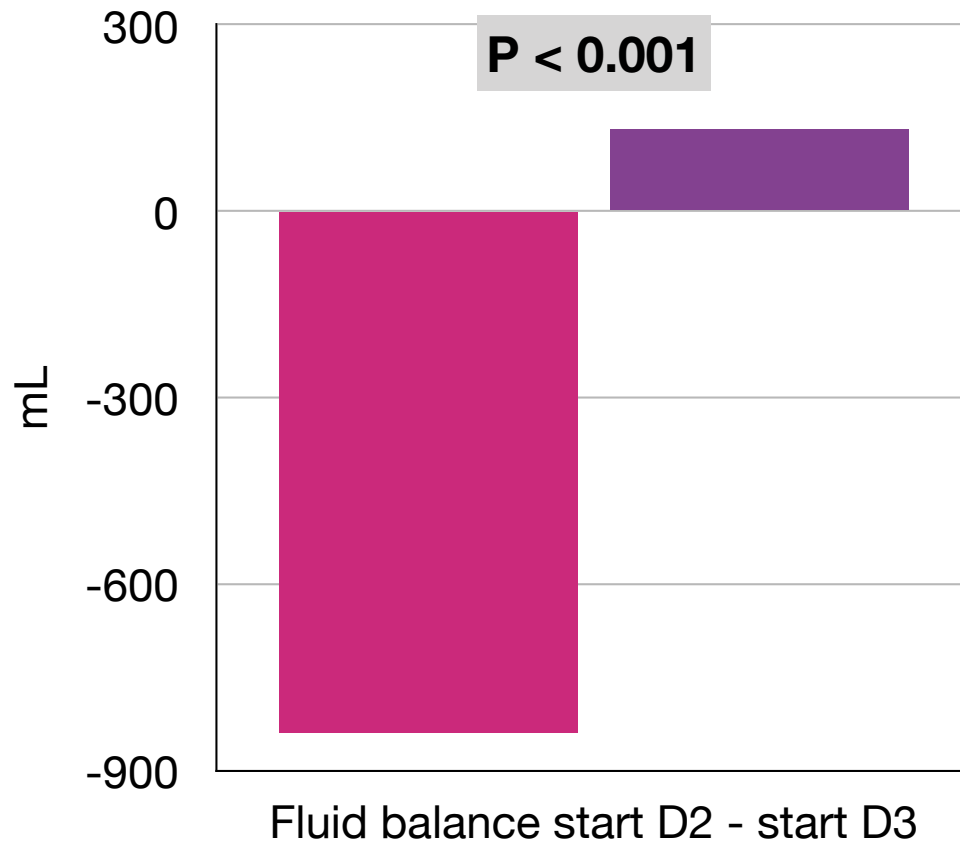
- Determine which patients actually benefit from early mobilization including longterm outcome measures
- Optimize phrenic nerve stimulation (number and intensity) and investigate if early start in patients who do not tolerate assisted ventilation may prevent diaphragm weakness

Feasibility of early restrictive fluid policy / deresuscitation (RADAR-2)

N = 179

Restrictive Control

More patients in restrictive group adverse events
No differences in VFD's, RRT, cognitive dysfunction



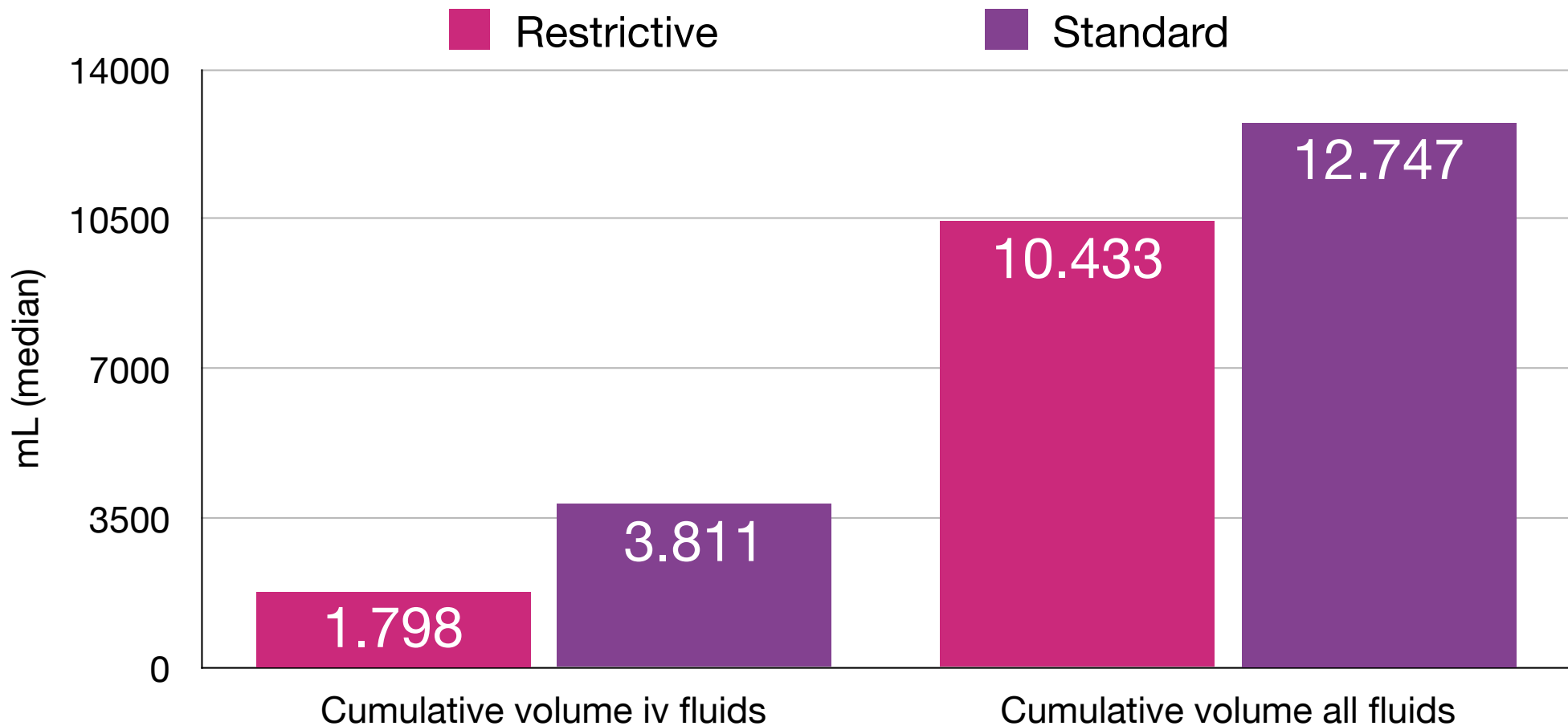
Cumulative balance D5 also lower

Fluid restriction in septic shock (CLASSIC trial)

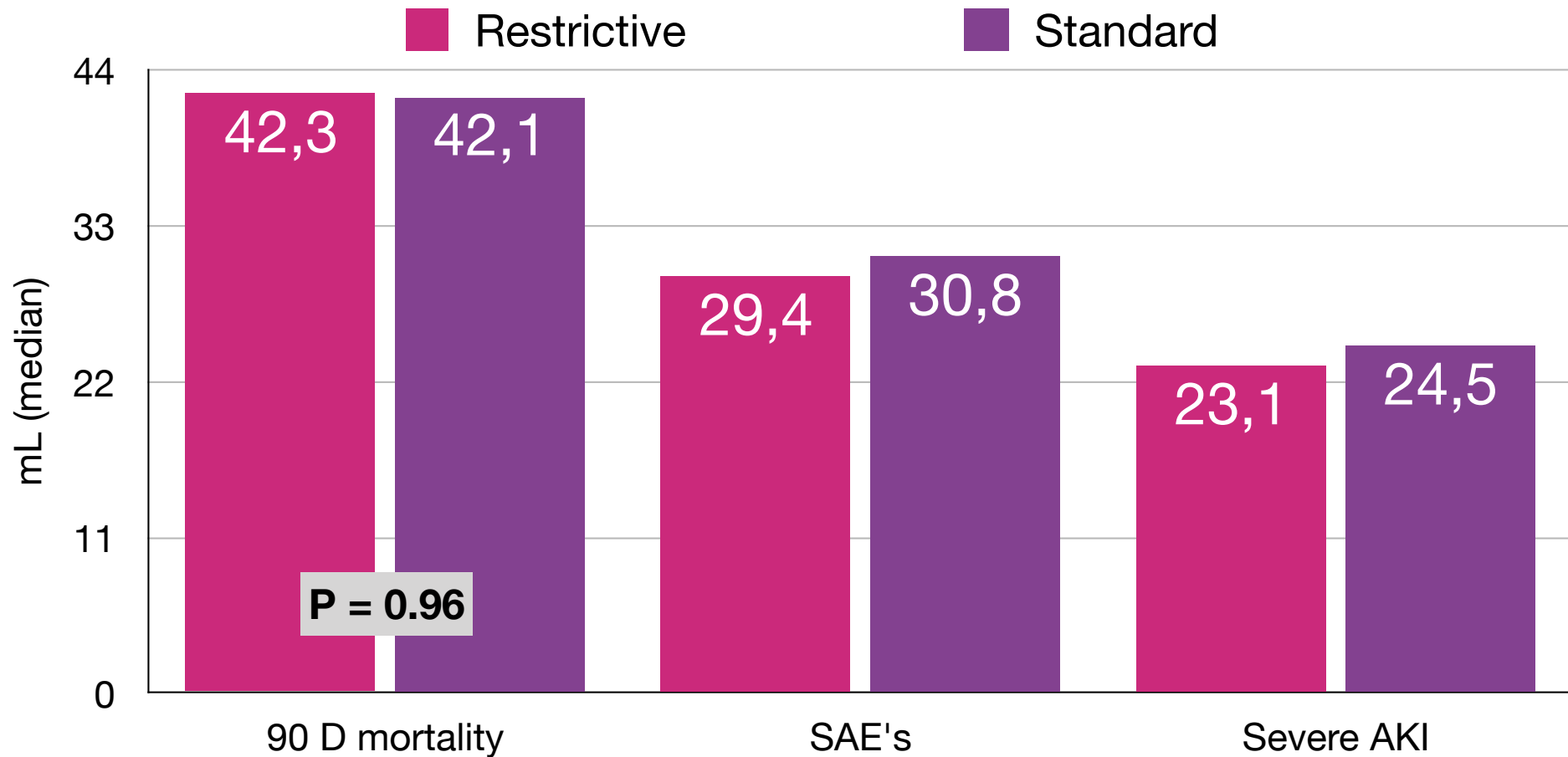
- MC (N=31) open-label RCT in adult ICU patients with early septic shock (< 12 hrs) comparing restrictive to standard iv fluid therapy for complete ICU stay or max 90 D
- Stratification for trial site and presence of metastatic or hematologic cancer
- Restrictive: only in case of severe hypoperfusion (lactate > 4, MAP < 50, mottling > 2, severe oliguria), replacement of fluid loss, correction of dehydration, in case enteral route contraindicated - standard: SSC 2016, fluid loss or dehydration, maintenance
- Primary outcome: death within 90 D - multiple secondary outcomes

Fluid restriction in septic shock (CLASSIC trial)

Total of 1545 patients included



Fluid restriction in septic shock (CLASSIC trial)



No differences in days alive without life support or out of hospital at D90

Restrictive fluid management in sepsis induced hypotension

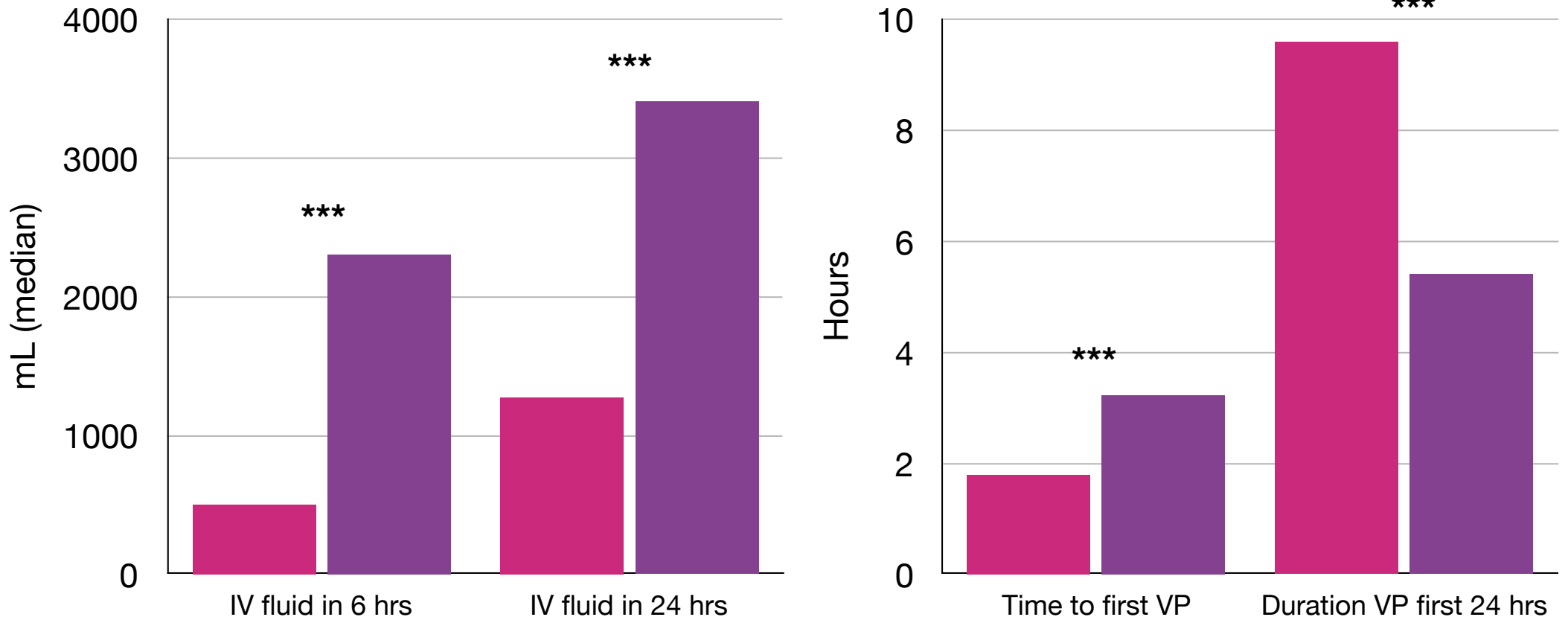
- MC unblinded RCT in adult patients with sepsis induced hypotension (RRsys < 100 mmHg despite \geq 1000 mL of iv fluids) comparing restrictive fluid administration with early vasopressors vs liberal fluid therapy for 24 hrs (initial dose 2000 mL - amendment allowed restriction to 1000 mL if stable)
- Exclusion criteria: receipt of > 3000 mL fluids in previous 24 hrs and severe fluid depletion from non-sepsis causes
- Primary outcome: Mortality D 90 before discharge home
- Multiple secondary outcomes

Restrictive fluid management in sepsis induced hypotension

Trial stopped for futility after 1563 patients (2320 intended)

Both groups received 2050 mL of fluid before randomization

Restrictive Liberal

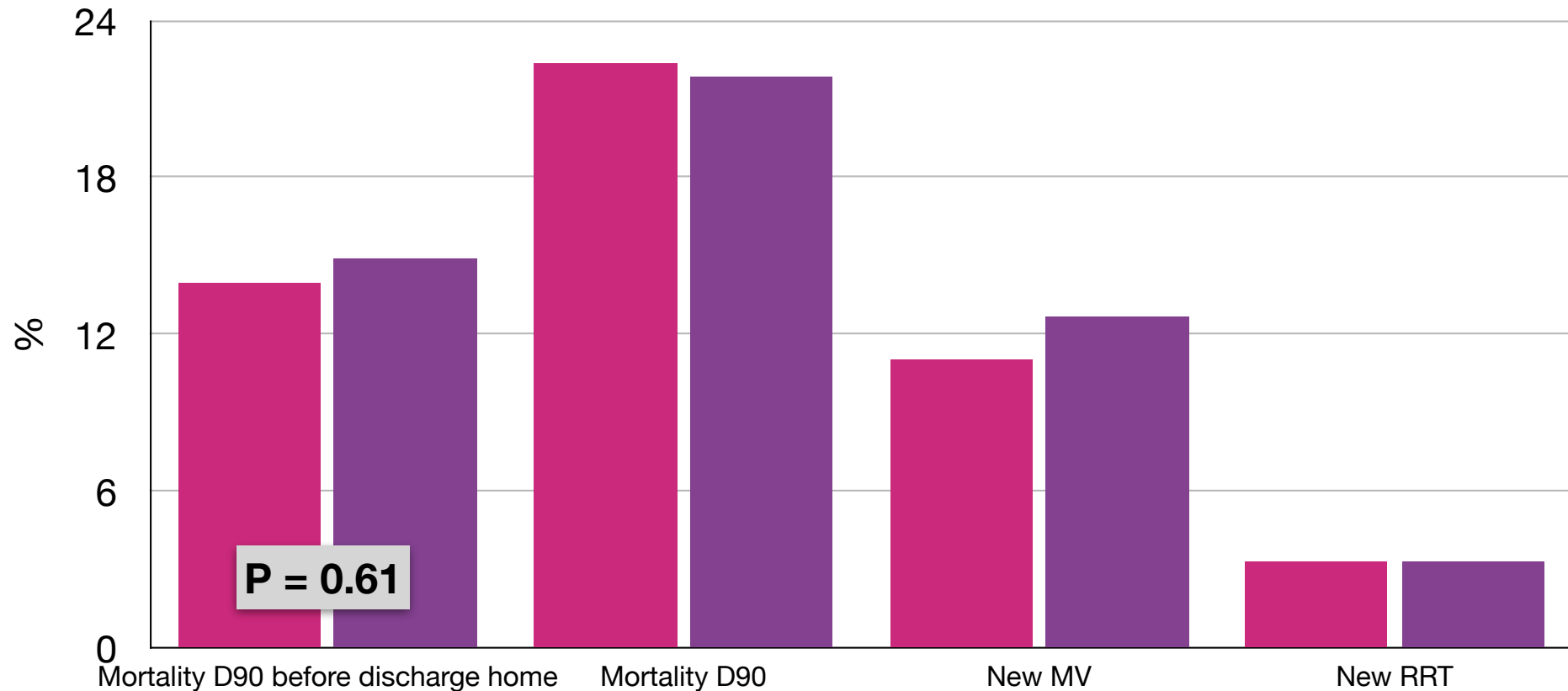


Overall total difference in 24 hrs **2100 mL**

Restrictive group more often VP

Shapiro NI (for the CLOVERS trial). N Eng J Med 2023 (published jan 21)

Restrictive fluid management in sepsis induced hypotension



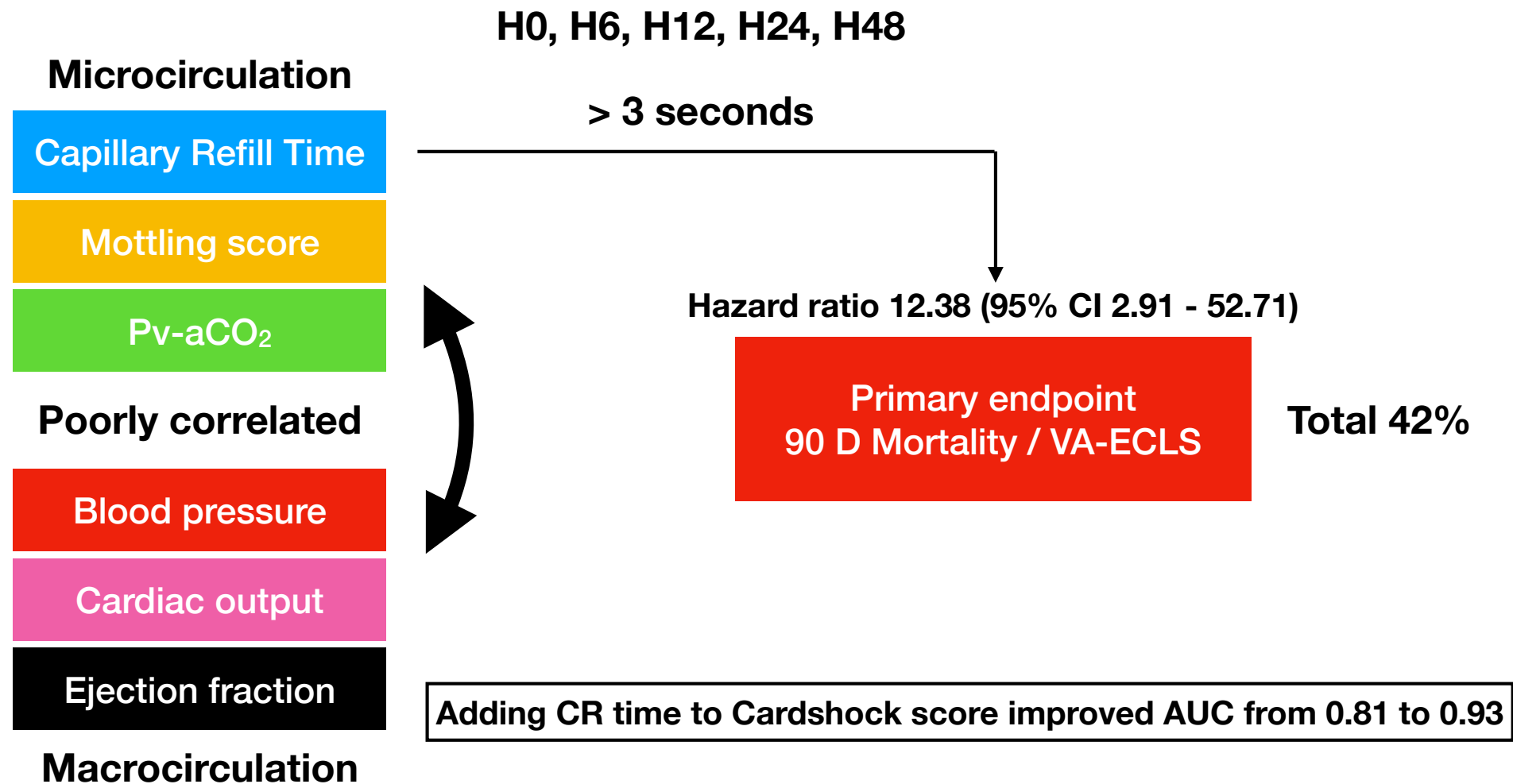
No differences in days free of organ support, new ARDS, LOS or SAE's

For the future

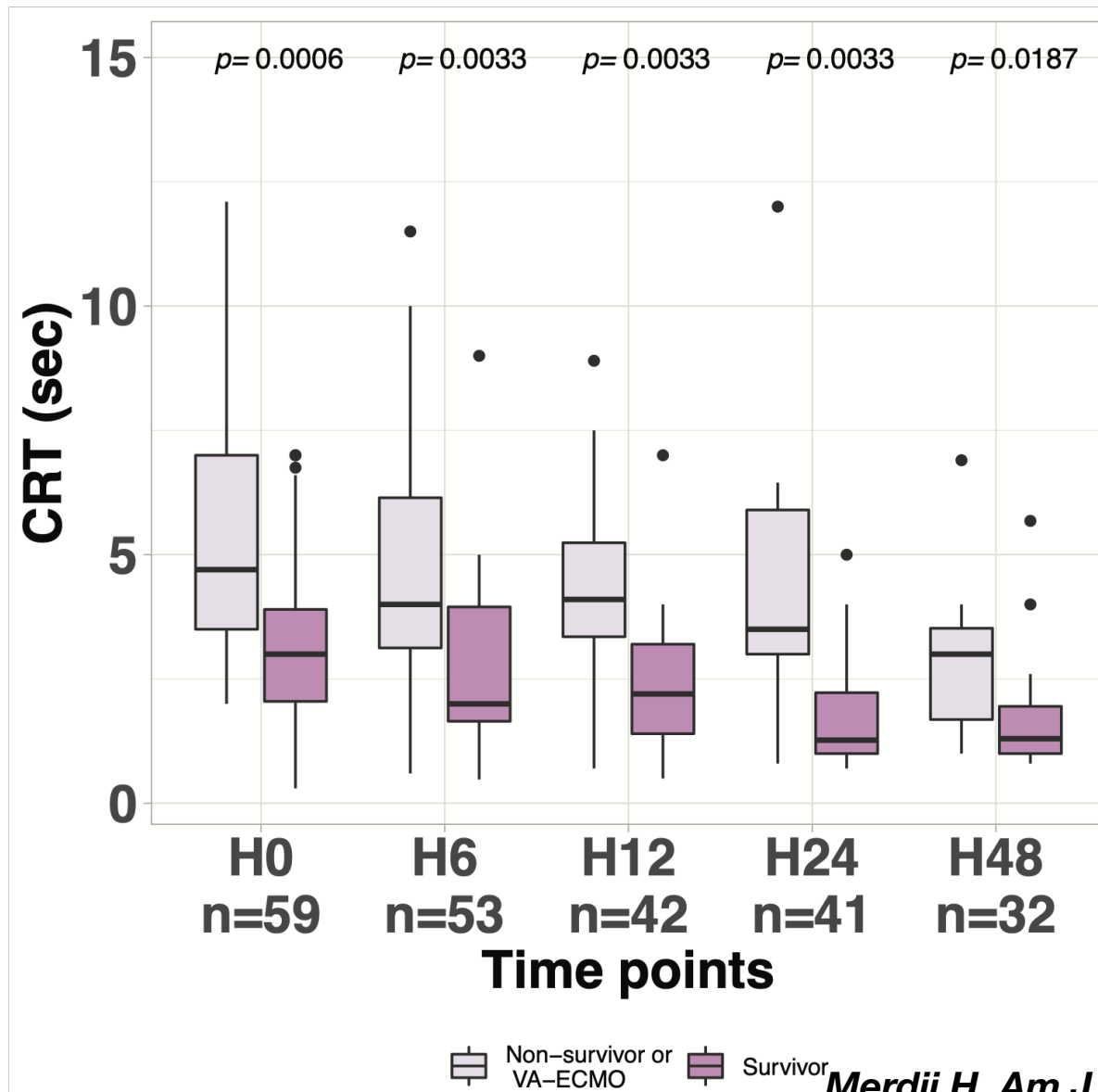
- Overall “restrictive” fluid policy in current practice makes it unlikely that further fluid restriction will be beneficial
- Fluid administration based on individualized easily measured clinical parameters (CRT, mottling score etc)

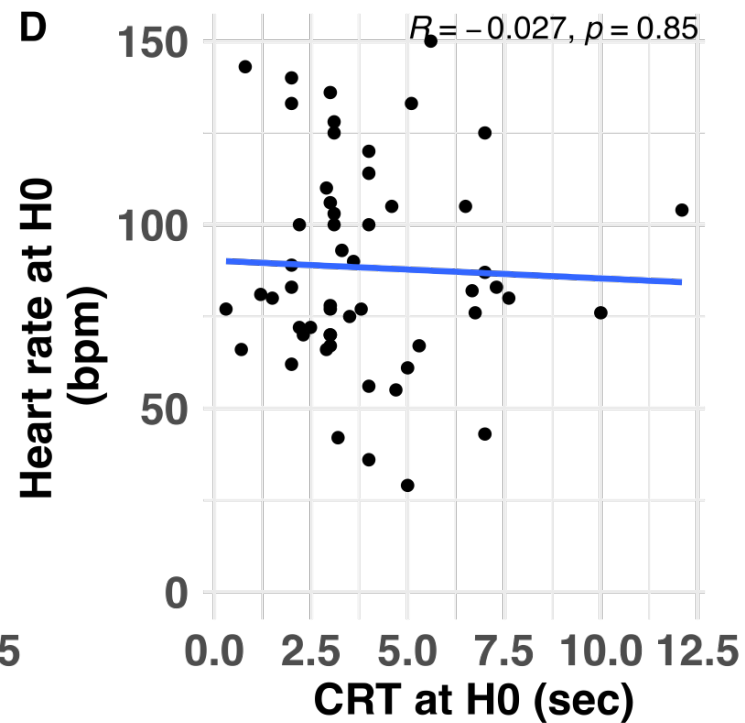
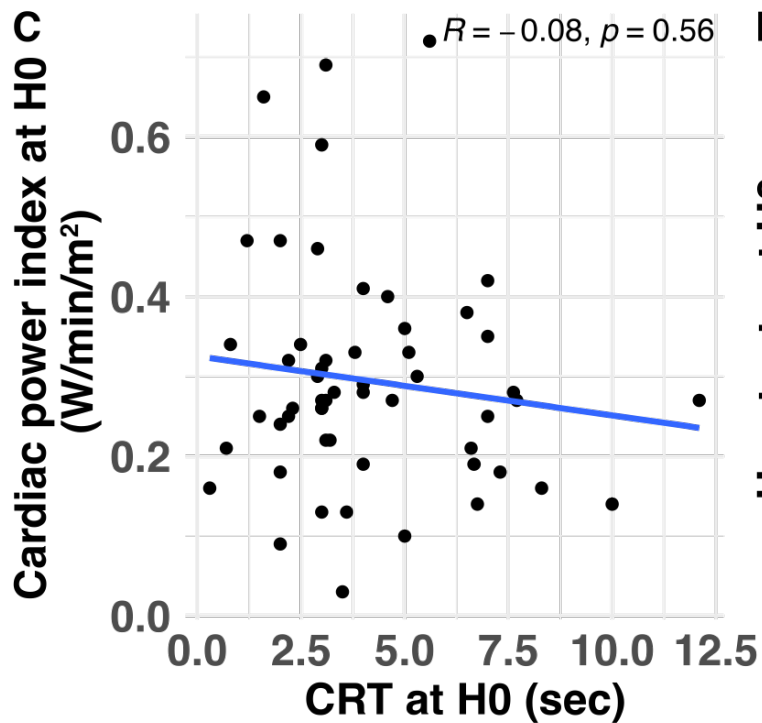
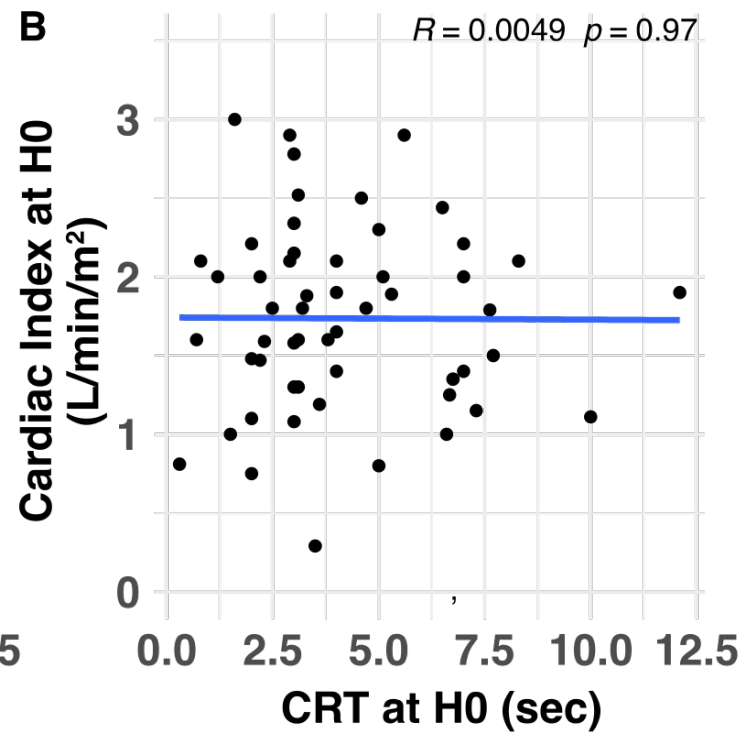
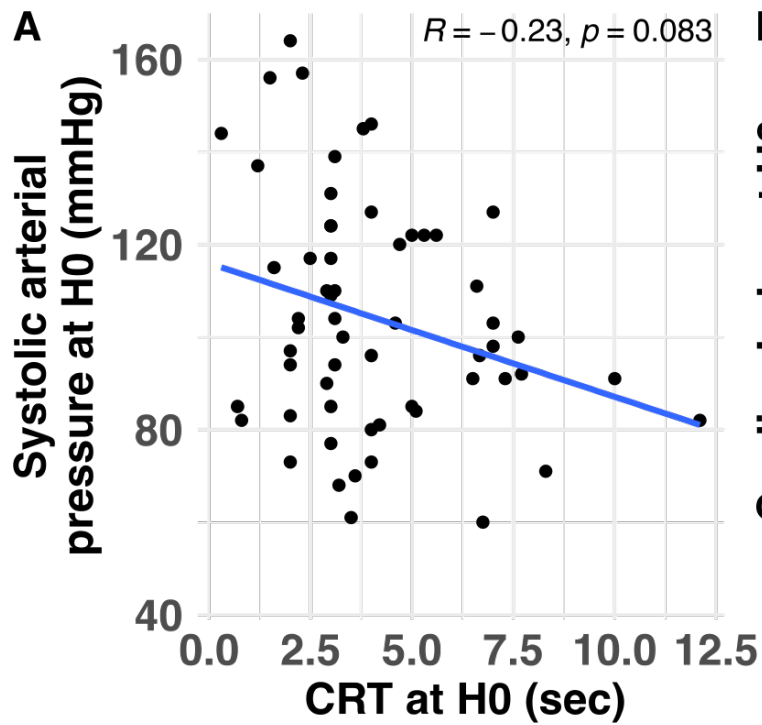
Disconcordance between macro- and microcirculation

61 patients with cardiogenic shock (59 analyzed)



CRT in cardiogenic shock



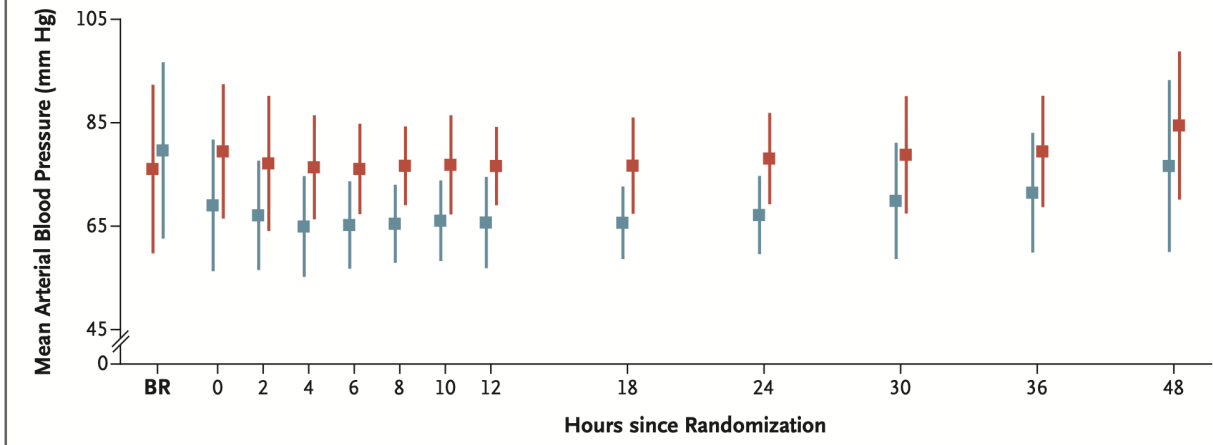


Optimal blood pressure after cardiac arrest

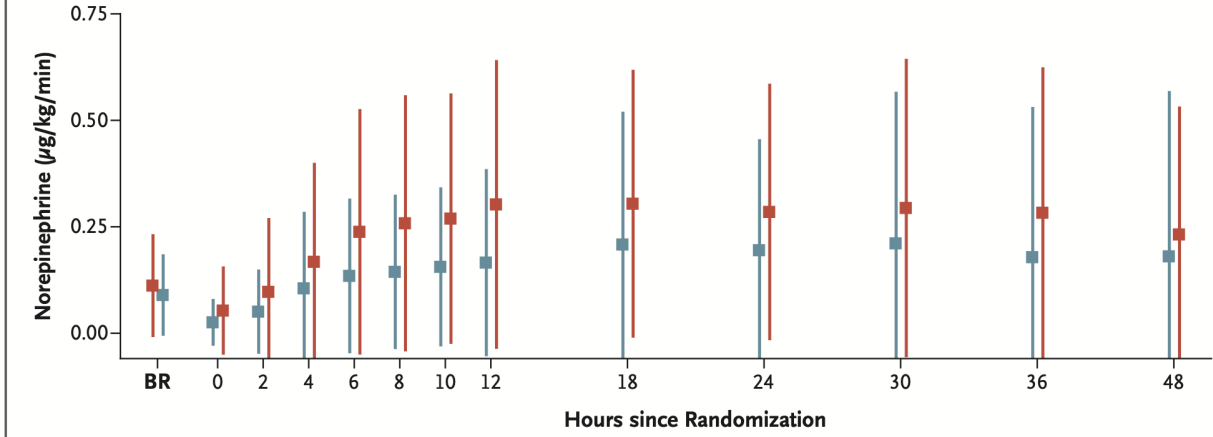
- DB RCT (2×2 factorial design) comparing MAP of 63 mmHg with 77 mmHg in 789 adult comatose survivors after OHCA (unwitnessed asystole excluded) treated with TTM
- All patients target MAP of 70 but half of modules measured 10% to low and the other half 10% to high
- Effects of 2 oxygen targets reported separately
- Primary outcome: composite of death or discharge with CPC 3/4 within D90
- Secondary outcome: NSE levels at 48 hrs, death from any cause, Montreal Cognitive Assessment and Rankin scale assessment and CPC at 3 months

Low blood-pressure target High blood-pressure target

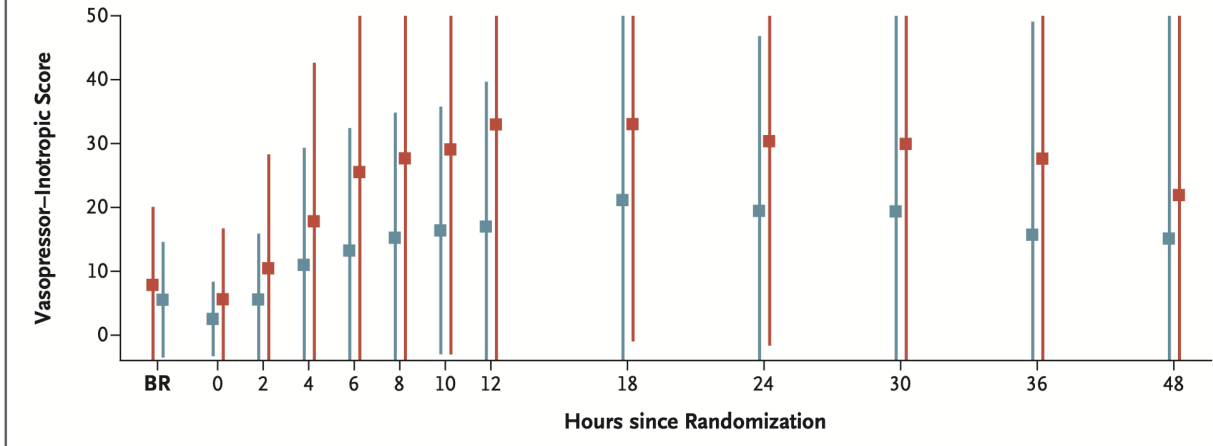
A Mean Arterial Blood Pressure



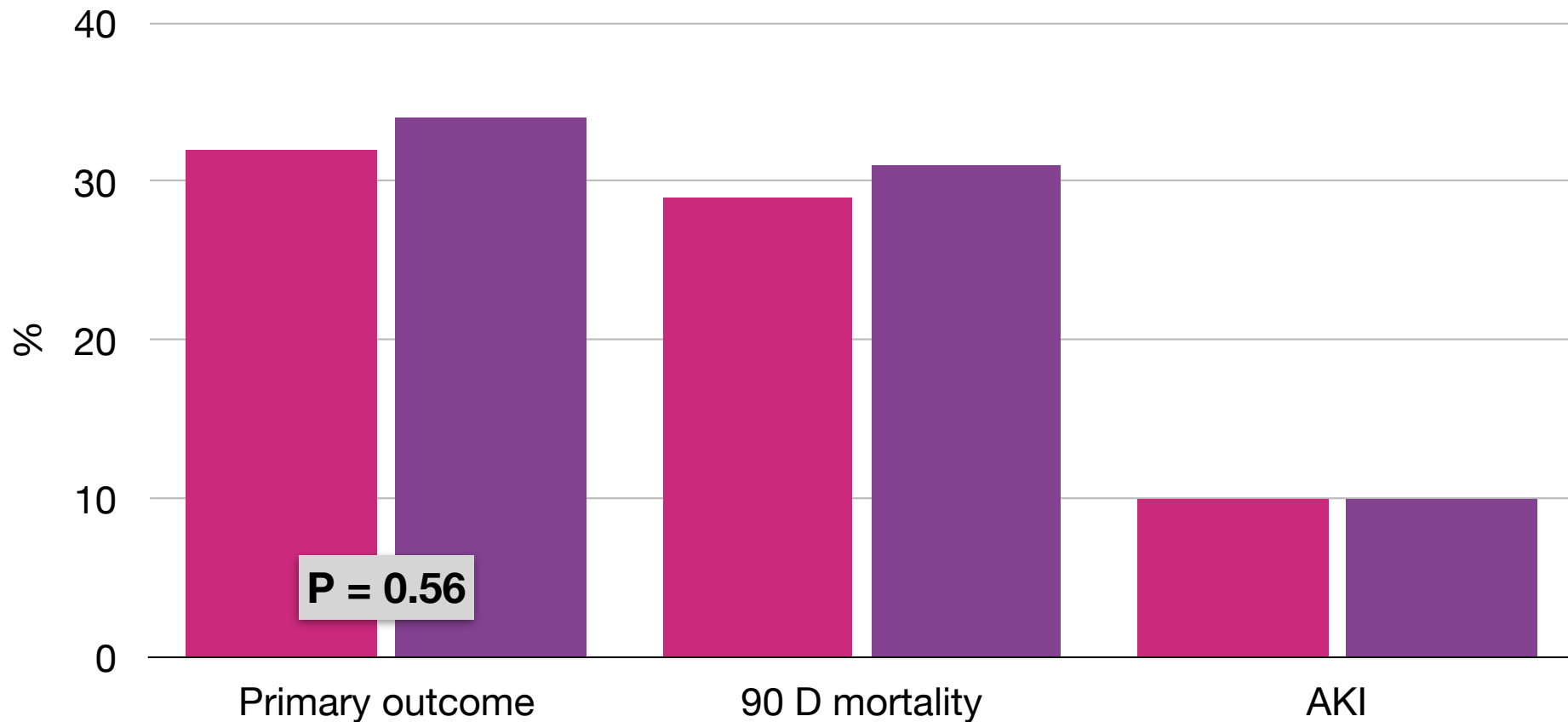
B Dose of Norepinephrine



C Vasopressor-Inotropic Score



Optimal blood pressure after cardiac arrest



No differences in CPC, mRS or MCA score at 3 months, NSE or SAE's

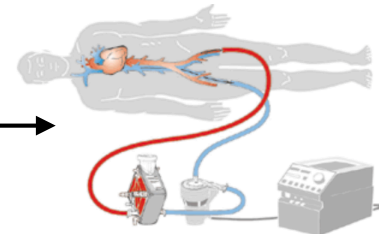
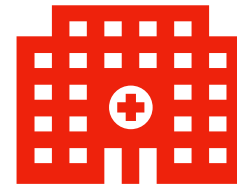
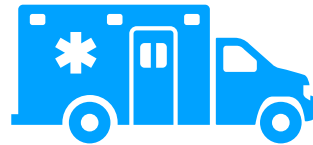
For the future

- Blood pressure target based on individualized parameters estimating optimal autoregulation (e.g. ORx)

RCT of eCPR in OHCA

Single centre (Prague)

N = 124



Declared dead 1

9
Cross
over
11

Refractory OHCA



Continued ACLS on site

Declared dead 45



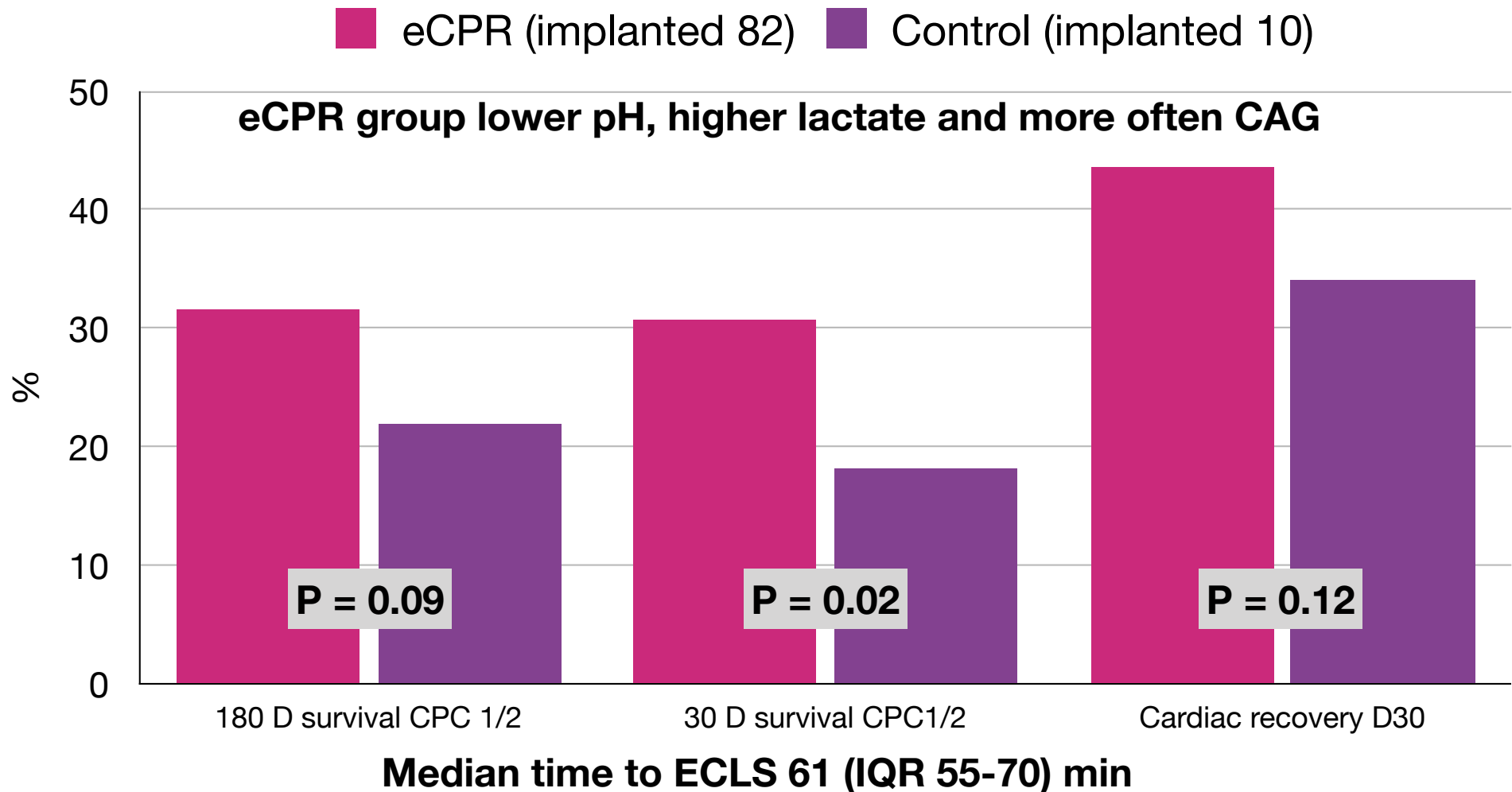
N = 132

Adults aged 18 - 65
Witnessed OHCA
Presumed cardiac etiology
> 5 minutes of ACLS

Primary outcome: 180 D survival with CPC 1-2

RCT of eCPR in OHCA

Stopped prematurely for futility



Major bleeding 31 vs 15%

Of all patients who received eCPR 22% had CPC1/2 at D180

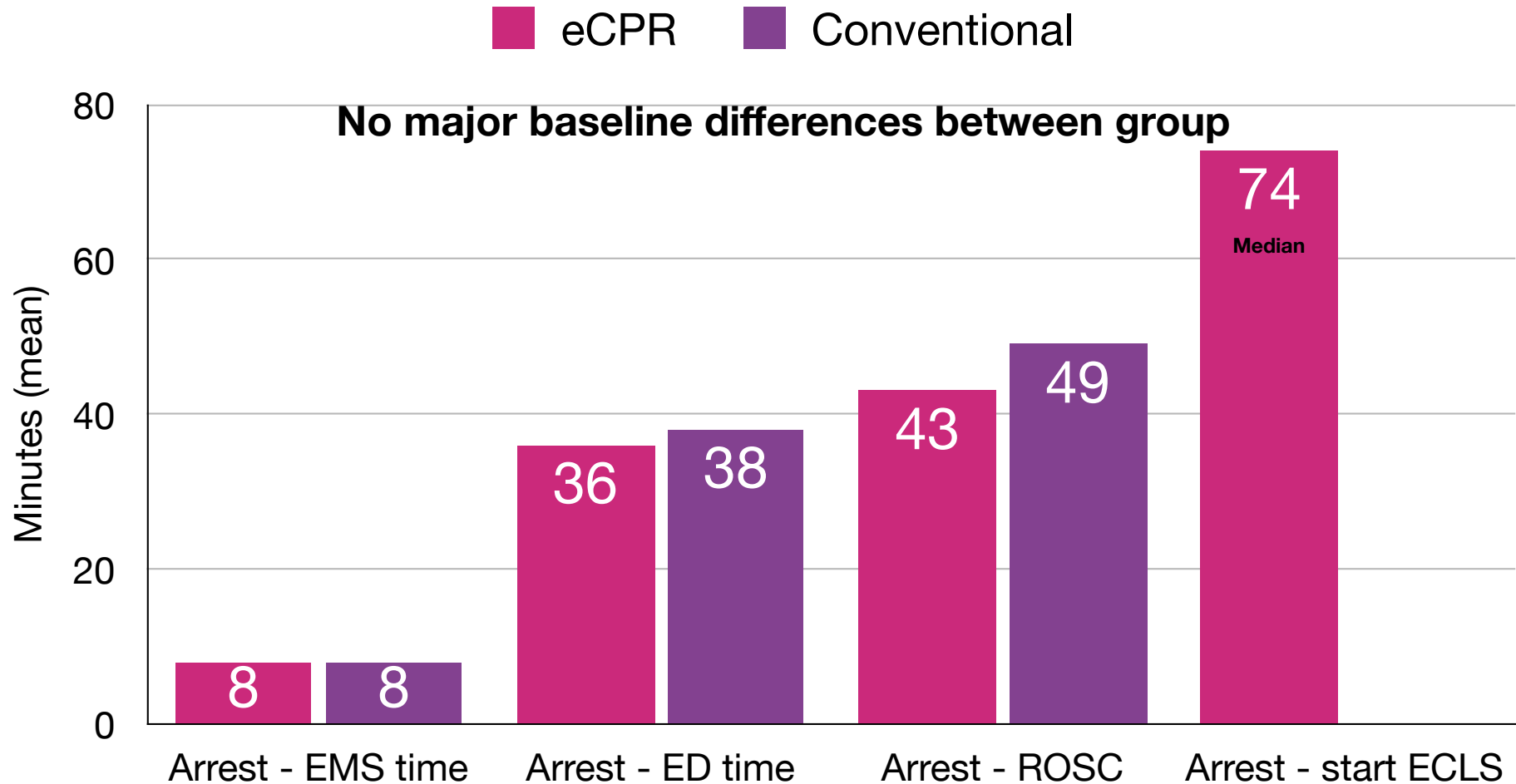
Belohlavek J. JAMA 2022;327:737-747

eCPR for refractory OHCA

- MC (N=10) RCT (1:1) in patients (age 18 - 70) with witnessed refractory (ACLS > 15 min) OHCA and initial shockable rhythm
- Multiple exclusion criteria including expected interval > 60 min between arrest and initiation canulation procedure
- Intention-to-treat analysis
- Primary outcome: 30 D survival with favorable neurologic outcome (CPC 1 or 2)
- Multiple secondary outcomes including LOS and LT survival

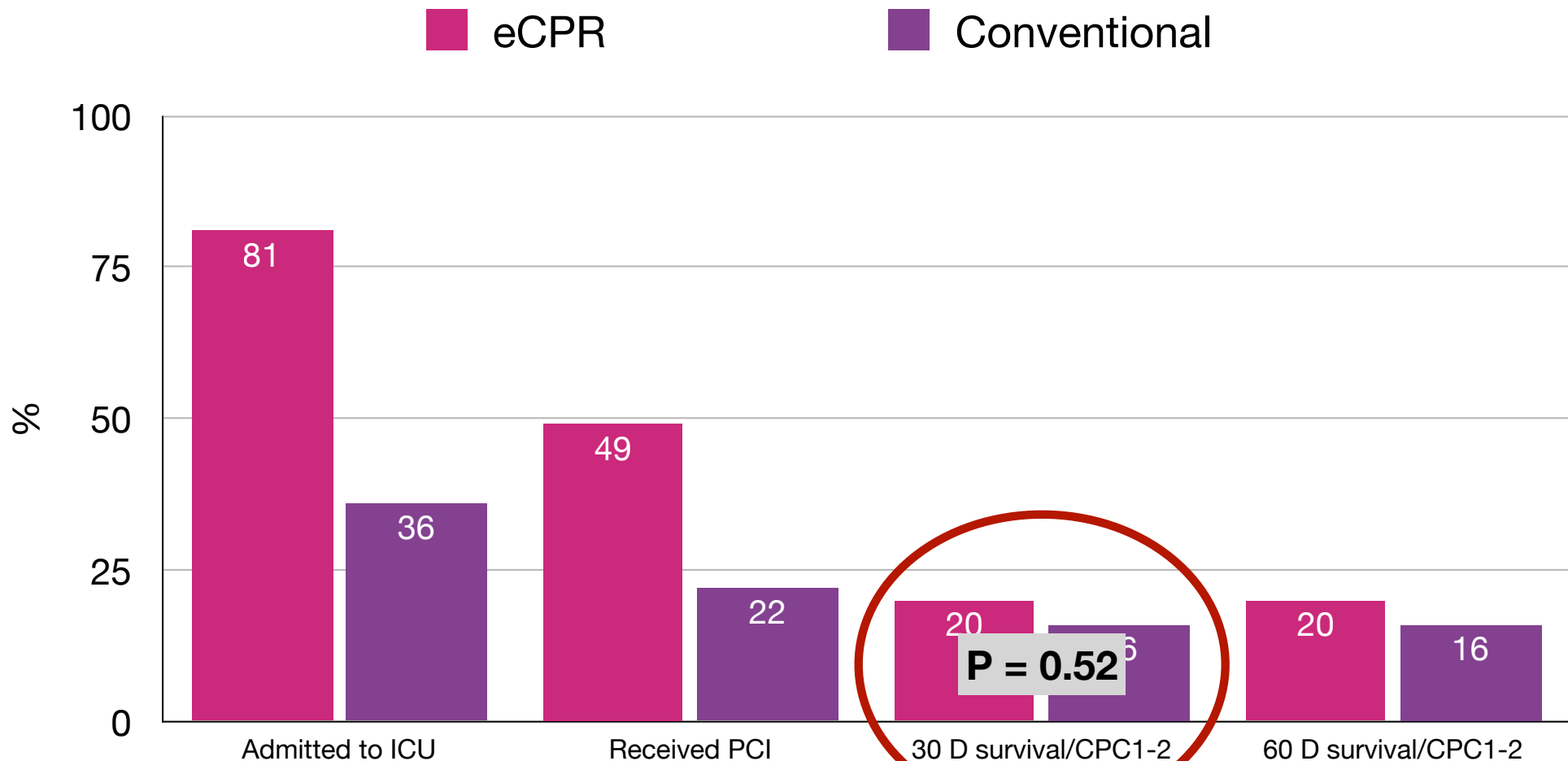
eCPR for refractory OHCA

160 patients randomized - 26 excluded on hospital arrival



eCPR for refractory OHCA

Of 70 patients randomized to eCPR only 46 received eCPR
Of 64 patients in control group 3 received eCPR



No indications of hospital costs

For the future

- Decrease time between arrest and effective eCPR (cancelation on site)
- Better determine which patients actually benefit from eCPR
- Optimal eCPR flow characteristics for optimal brain perfusion
- Pharmacological protection of brain until start eCPR

Balanced fluids in the ICU - The PLUS study

- DB MC (N = 53) RCT in adult patients expected to be on the ICU for 3 consecutive days comparing NaCl 0.9% with Plasma-Lyte 148 (TBI excluded)
- Patients received the assigned trial fluid for up to 90 days after randomization unless they were discharged from the ICU
- Primary outcome: all cause death within 90 D (also in 6 pre-defined subgroups)
- Multiple secondary outcomes

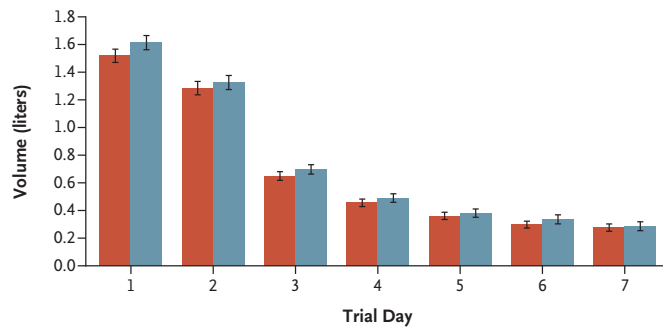
Balanced fluids in the ICU - The PLUS study

Total of 4846 patients - originally 8800 intended
No differences in baseline characteristics

Median duration of treatment 6 days - volume 3.9 L (balanced), 3.7 L NaCL 0.9%

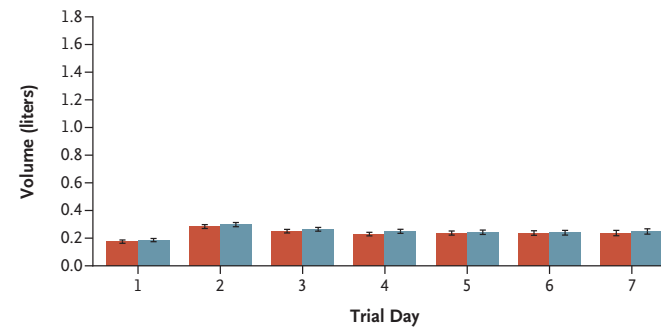
■ Saline group ■ BMES group

A Concealed Trial Fluid Received in Each Group as Assigned



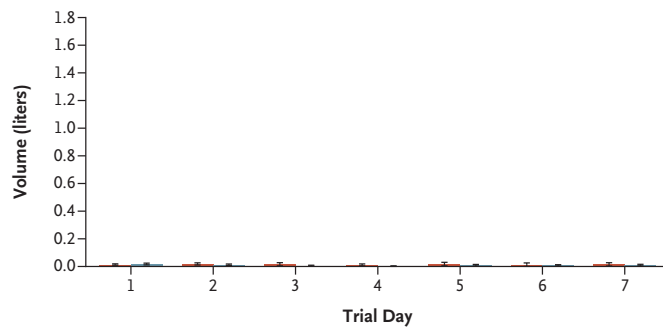
No. of Patients	1	2	3	4	5	6	7
Saline group	2446	2389	2154	1790	1412	1160	950
BMES group	2450	2393	2148	1783	1430	1166	938

B Open-Label Saline Solution Received in Each Group



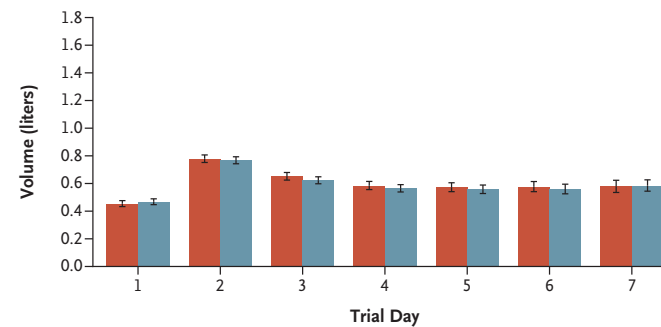
No. of Patients	1	2	3	4	5	6	7
Saline group	2324	2273	2050	1710	1344	1105	906
BMES group	2330	2275	2040	1700	1361	1114	894

C Open-Label BMES Received in Each Group



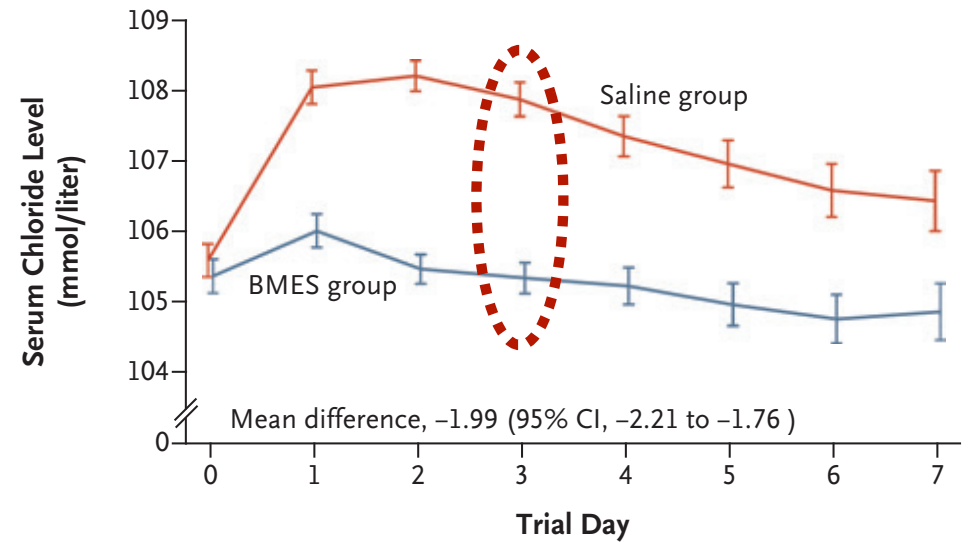
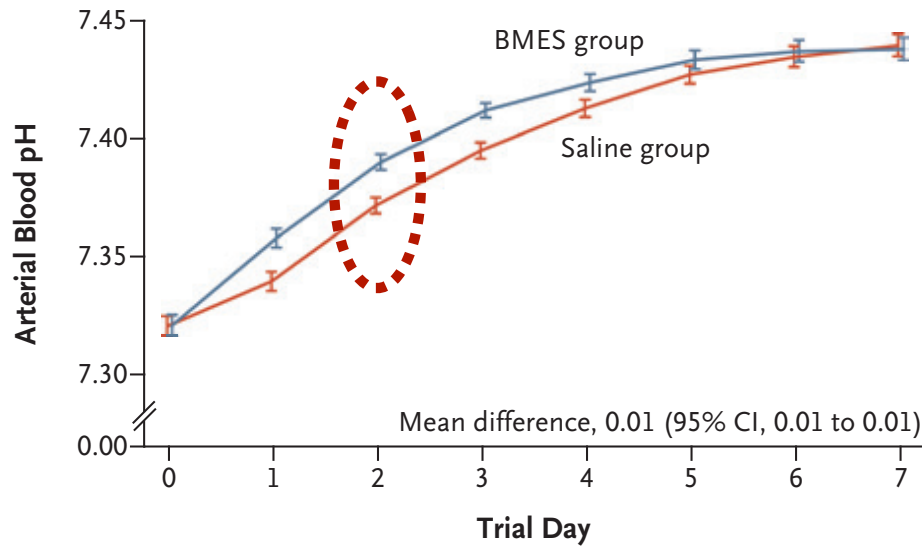
No. of Patients	1	2	3	4	5	6	7
Saline group	2324	2273	2050	1710	1344	1105	906
BMES group	2330	2275	2040	1700	1361	1114	894

D Other Open-Label Crystalloid Fluids Received in Each Group



No. of Patients	1	2	3	4	5	6	7
Saline group	2324	2273	2050	1710	1344	1105	906
BMES group	2330	2275	2040	1700	1361	1114	894

Balanced fluids in the ICU - The PLUS study



No. of Patients

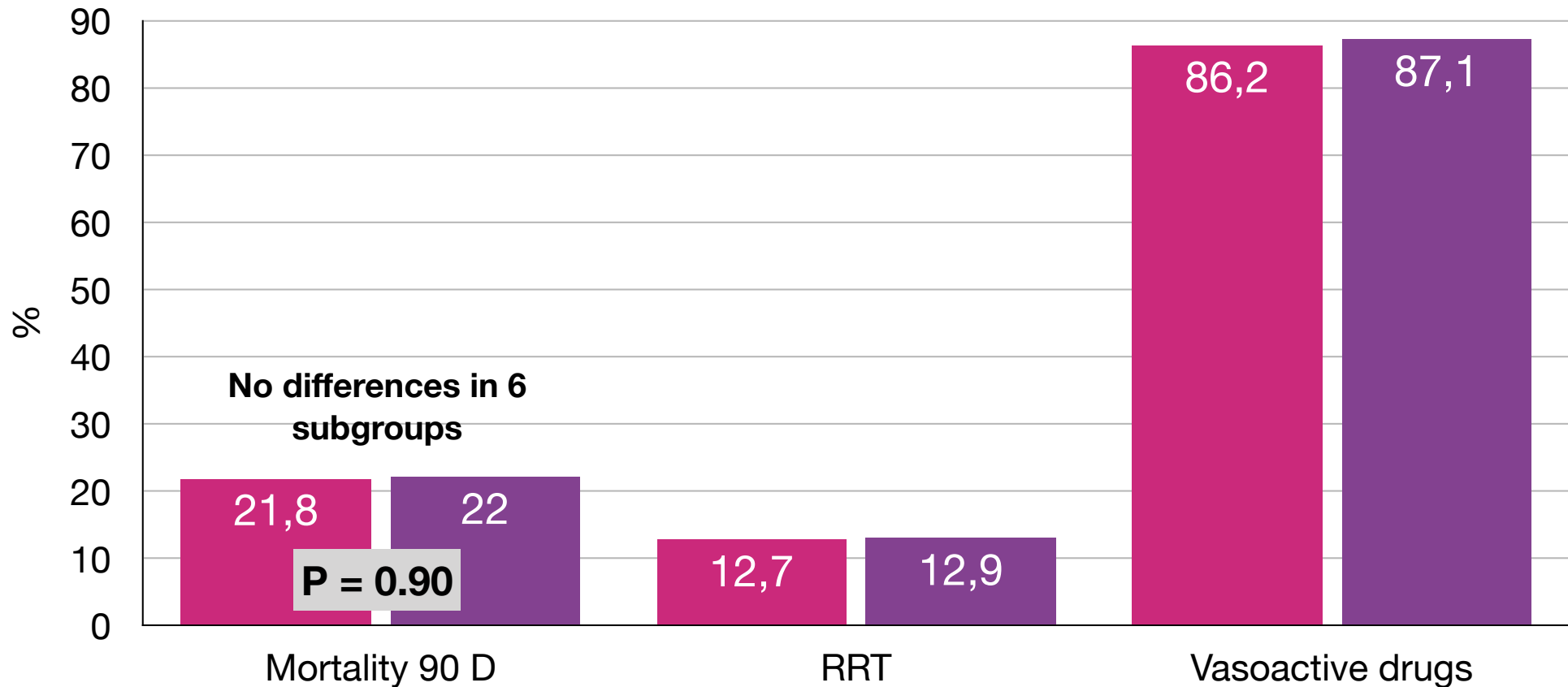
Saline group	2272	2092	2251	1837	1405	1067	862	704
BMES group	2280	2103	2223	1818	1402	1066	834	691

No. of Patients

Saline group	2410	1998	2344	2044	1679	1330	1088	884
BMES group	2413	1996	2337	2043	1664	1344	1095	875

Balanced fluids in the ICU - The PLUS study

No differences in severe adverse effects

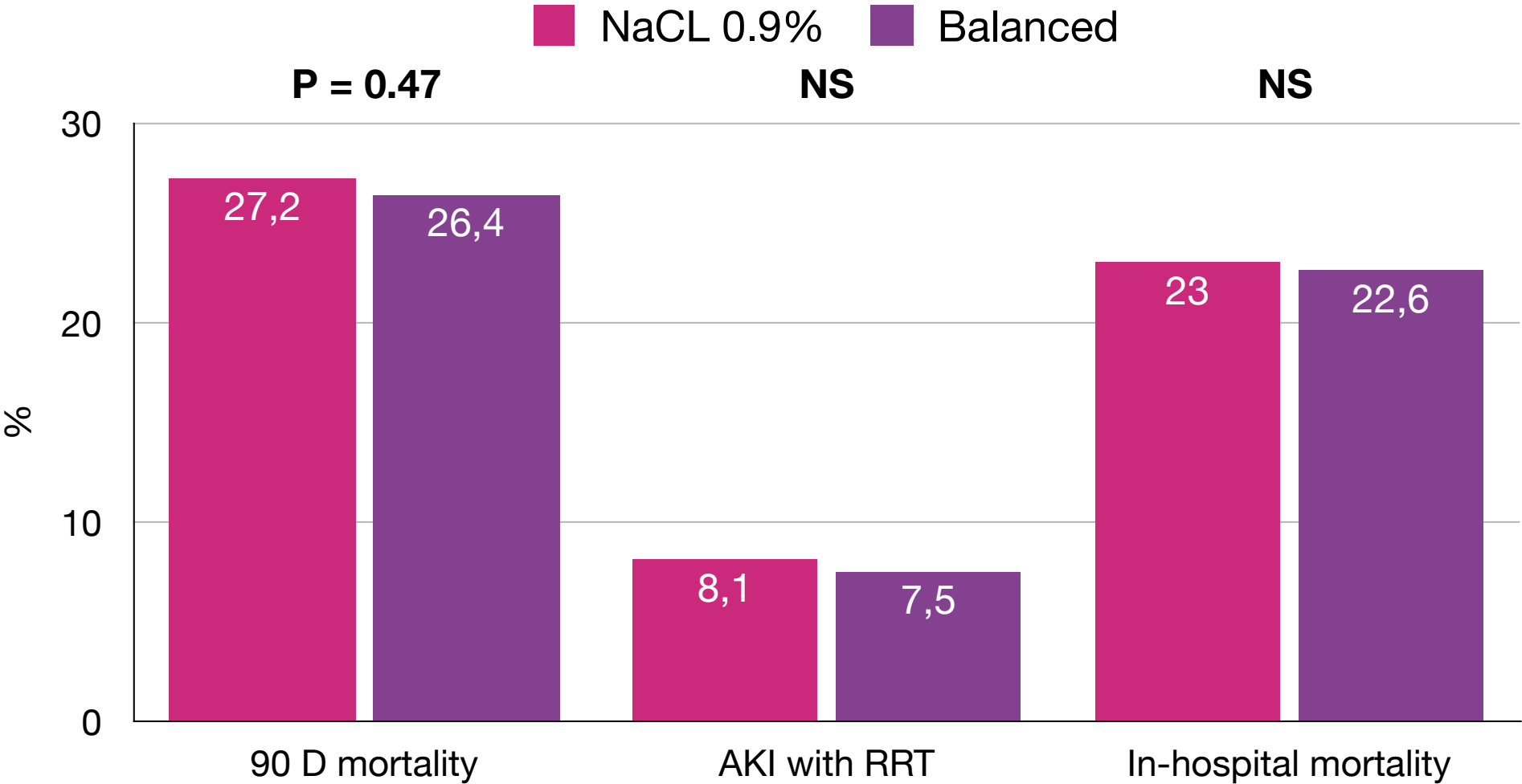


No differences in days alive without MV, vasoactive agents or outside hospital

Balanced fluid vs NaCl 0.9% - meta-analysis

- Meta-analysis of 6 low risk of bias trials with 34450 participants
- RR for 90 D mortality with balanced vs NaCl 0.9% was 0.96 (0.91 - 1.01)
- Bayesian analysis: posterior probability that balanced fluid reduce mortality was 89.5%
- RR for AKI was 0.96 (0.89 - 1.02) and RRT 0.95 (0.81 - 1.11)
- No differences in VFD's and vasopressor free days

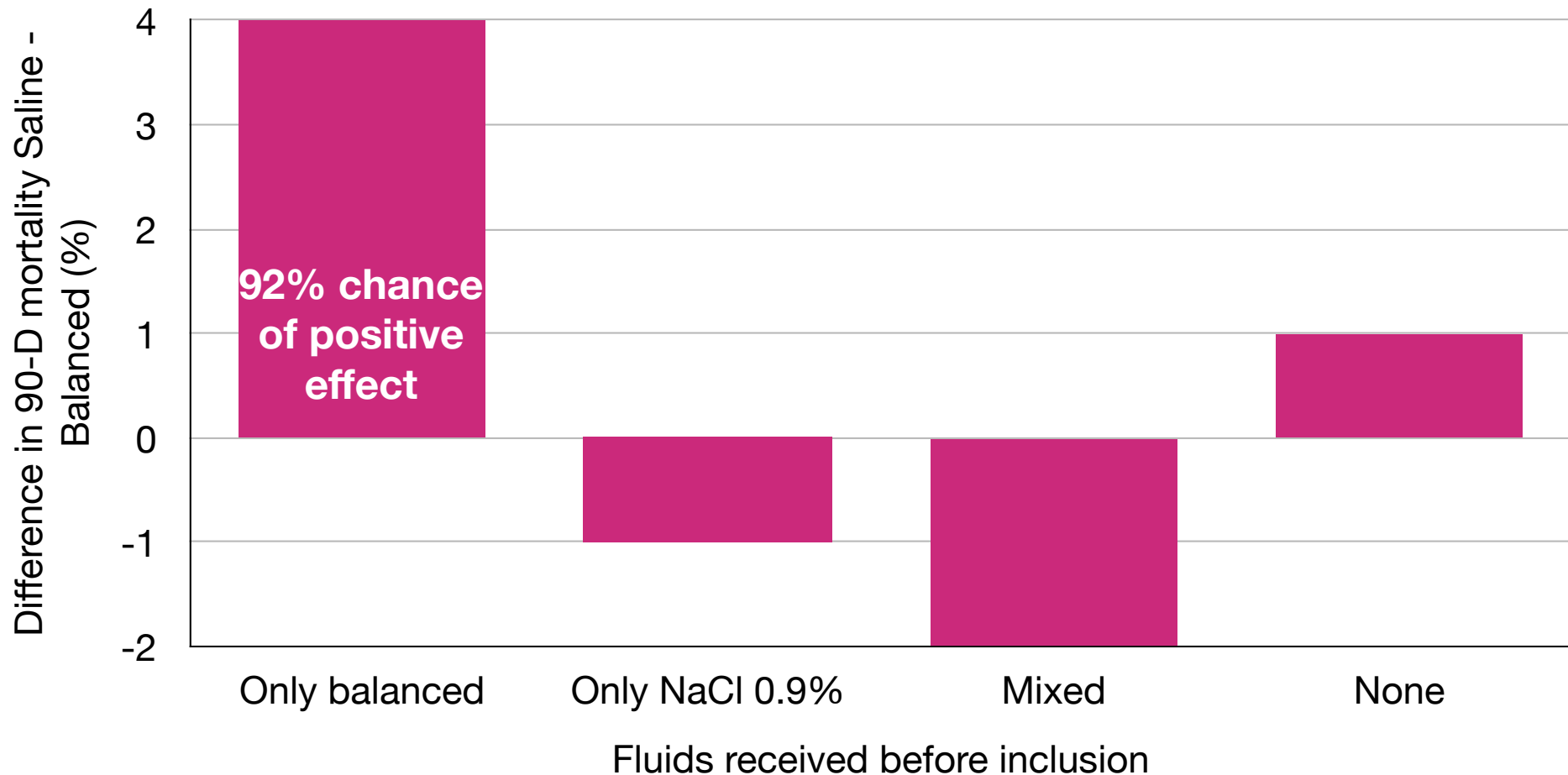
Balanced fluids in critically ill patients (BaSICS trial)



No differences in D28 VFD's, ICU LOS, Hospital LOS

Are the results influenced by pre-randomization therapy?

Do the fluids receive in the 24 hrs before enrollment influence outcome



For the future

- Personalized trial in which fluid administration is not based on balanced- or unbalanced fluids but on obtaining clear physiological goals (pH, chloride, sodium etc) depending on phase of the disease



24 november 2023