LÉKAŘSKÁ FAKULTA
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KLINIKA DĚTSKÉ
ANESTEZIOLOGIE
A RESUSCITACE

# Top 10 publikací v intenzivní medicíně

Milan Kratochvíl

FAKULTNÍ
NEMOCNICE
BRNO

# Poresuscitační péče a prognostikace

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 11, 2019 VOL. 380 NO. 15

# Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

J.S. Lemkes, G.N. Janssens, N.W. van der Hoeven, L.S.D. Jewbali, E.A. Dubois, M. Meuwissen, T.A. Rijpstra, H.A. Bosker, M.J. Blans, G.B. Bleeker, R. Baak, G.J. Vlachojannis, B.J.W. Eikemans, P. van der Harst, I.C.C. van der Horst, M. Voskuil, J.J. van der Heijden, A. Beishuizen, M. Stoel, C. Camaro, H. van der Hoeven, J.P. Henriques, A.P.J. Vlaar, M.A. Vink, B. van den Bogaard, T.A.C.M. Heestermans, W. de Ruijter, T.S.R. Delnoij, H.J.G.M. Crijns, G.A.J. Jessurun, P.V. Oemrawsingh, M.T.M. Gosselink, K. Plomp, M. Magro, P.W.G. Elbers, P.M. van de Ven, H.M. Oudemans-van Straaten, and N. van Royen

COACT trial

N Engl J Med 2019;380:1397-407.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 11, 2019 VOL. 380 NO. 15

Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

# Design

- Východiska: doporučení ESC, CCF/AHA – okamžitá PCI u pacientů po CA
- Multicentrická randomizovaná nezaslepená studie
- 538 pacientů – defibrilovatelný rytmus, persistující bezvědomí, bez známek STEMI

N Engl J Med 2019;380:1397-407.

The NEW ENGLAND JOURNAL of MEDICINE

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Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

# Intervence

- Včasná (<2 hodin) koronarografie vs. odložená (po neurologickém zotavení, nebo po propuštění z ICU)

N Engl J Med 2019;380:1397-407.

The NEW ENGLAND JOURNAL of MEDICINE

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Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

# Outcome

- Primární : 90- denní mortalita
- Sekundární:
  - 90- denní mortalita s dobrým CPC
  - Troponin, CK, CK-MB
  - AKI, CRRT
  - Neurologický stav při propuštění z ICU
  - Trvání vasopresorů a inotropik
  - Šok
  - Trvání UPV
  - Krvácení dle TIMI

N Engl J Med 2019;380:1397-407.

**Table 2. Procedures, Treatments, and Characteristics of Coronary Artery Disease.***

| Variable | Immediate Angiography Group (N=273) | Delayed Angiography Group (N=265) |
|---|---|---|
| Coronary angiography performed — no. (%) | 265 (97.1) | 172 (64.9)† |
| Median time from arrest to coronary angiography (IQR) — hr | 2.3 (1.8–3.0) | 121.9 (52.0–197.3) |
| Median time from randomization to coronary angiography (IQR) — hr | 0.8 (0.5–1.2) | 119.9 (47.2–203.7) |
| Severity of coronary artery disease — no./total no. (%) | | |
| No clinically significant disease | 94/265 (35.5) | 59/172 (34.3) |
| One-vessel disease | 72/265 (27.2) | 49/172 (28.5) |
| Two-vessel disease | 54/265 (20.4) | 35/172 (20.3) |
| Three-vessel disease | 45/265 (17.0) | 29/172 (16.9) |
| Acute unstable lesion — no./total no. (%)‡ | 36/265 (13.6) | 29/172 (16.9) |
| Acute thrombotic occlusion — no./total no. (%) | 9/265 (3.4) | 13/172 (7.6)§ |
| Chronic total occlusion — no./total no. (%) | 100/265 (37.7) | 58/172 (33.7) |
| Revascularization treatment — no. (%) | | |
| PCI | 90 (33.0) | 64 (24.2) |
| CABG | 17 (6.2) | 23 (8.7) |
| Pharmacologic or conservative treatment | 168 (61.5) | 179 (67.5) |

N Engl J Med 2019;380:1397-407.

**Table 3. Clinical Outcomes.***

| Outcome | Immediate Angiography Group (N=273) | Delayed Angiography Group (N=265) | Effect Size (95% CI)† |
|---|---|---|---|
| **Primary end point** | | | |
| Survival at 90 days — no. of patients (%)‡ | 176 (64.5) | 178 (67.2) | OR, 0.89 (0.62 to 1.27) |
| **Secondary end points** | | | |
| Survival with good cerebral performance or mild or moderate disability — no. of patients/total no. (%) | 171/272 (62.9) | 170/264 (64.4) | OR, 0.94 (0.66 to 1.31) |
| CPC score at 90 days — no./total no. (%)§ | | | |
| 1 | 157/272 (57.7) | 159/264 (60.2) | Reference |
| 2 | 14/272 (5.1) | 11/264 (4.2) | OR, 1.29 (0.56 to 2.92) |
| 3 | 4/272 (1.5) | 5/264 (1.9) | OR, 0.81 (0.21 to 3.07) |
| 4 | 0/272 | 2/264 (0.8) | NA |
| 5 | 97/272 (35.7) | 87/264 (33.0) | OR, 1.13 (0.78 to 1.63) |
| Survival until hospital discharge — no. of patients (%) | 178 (65.2) | 182 (68.7) | OR, 0.85 (0.60 to 1.22) |
| Neurologic status at ICU discharge | | | |
| GCS score | | | |
| Median (IQR) | 15 (14 to 15) | 15 (14 to 15) | |
| Geometric mean (95% CI) | 13.7 (13.2 to 14.2) | 13.5 (12.9 to 13.7) | 1.02 (0.96 to 1.04) |
| CPC score — no./total no. (%)§ | | | |
| 1 | 74/258 (28.7) | 86/249 (34.5) | Reference |
| 2 | 59/258 (22.9) | 56/249 (22.5) | OR, 1.22 (0.76 to 1.98) |
| 3 | 36/258 (14.0) | 30/249 (12.0) | OR, 1.39 (0.78 to 2.48) |
| 4 | 4/258 (1.6) | 9/249 (3.6) | OR, 0.52 (0.15 to 1.75) |
| 5 | 85/258 (32.9) | 68/249 (27.3) | OR, 1.45 (0.93 to 2.27) |

N Engl J Med 2019;380:1397-407.

The NEW ENGLAND JOURNAL of MEDICINE

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Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

# Nedostatky

- Nezaslepená studie
- Nebyly informace o průběhu skríningu – selection bias
- Vyřazení pacienti v šoku, renální insuficiencí
- Underpowered (nízká mortalita)
- Nehodnotili dlouhodobé kardiální outcomy

N Engl J Med 2019;380:1397-407.

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Coronary Angiography after Cardiac Arrest without ST-Segment Elevation

In conclusion, in this randomized, multicenter trial involving patients who were successfully resuscitated after out-of-hospital cardiac arrest and who had a shockable rhythm and no signs of STEMI or a noncoronary cause of the arrest, a strategy of immediate angiography was not better than a strategy of delayed angiography with respect to overall survival at 90 days.

N Engl J Med 2019;380:1397-407.

ORIGINAL ARTICLE

# Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

J.-B. Lascarrou, H. Merdji, A. Le Gouge, G. Colin, G. Grillet, P. Girardie, E. Coupez, P.-F. Dequin, A. Cariou, T. Boulain, N. Brule, J.-P. Frat, P. Asfar, N. Pichon, M. Landais, G. Plantefeve, J.-P. Quenot, J.-C. Chakarian, M. Sirodot, S. Legriel, J. Letheulle, D. Thevenin, A. Desachy, A. Delahaye, V. Botoc, S. Vimeux, F. Martino, B. Giraudeau, and J. Reignier, for the CRICS-TRIGGERSEP Group*

HYPERION

DOI: 10.1056/NEJMoa1906661

ORIGINAL ARTICLE

# Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

J.-B. Lascarrou, H. Merdji, A. Le Gouge, G. Colin, G. Grillet, P. Girardie,

# Design

- Nezaslepená, (zaslepený hodnotitel outcomu), pragmatická, multicentrická randomizovaná studie
- 25 ICU Francie 581 pacientů
- Inclusion:
  - pacienti >18let, OHCA/IHCA, komatózní, nedefibrilovatelný rytmus
- Exclusion:
  - no-flow >10 minut; low-flow >60 minut; závažná oběhová instabilita (adrenalin, nebo noradrenalin >1 µg/kg/min); CA do skríningu >300 minut; moribunní; Child–Pugh C

DOI: 10.1056/NEJMoa1906661

ORIGINAL ARTICLE

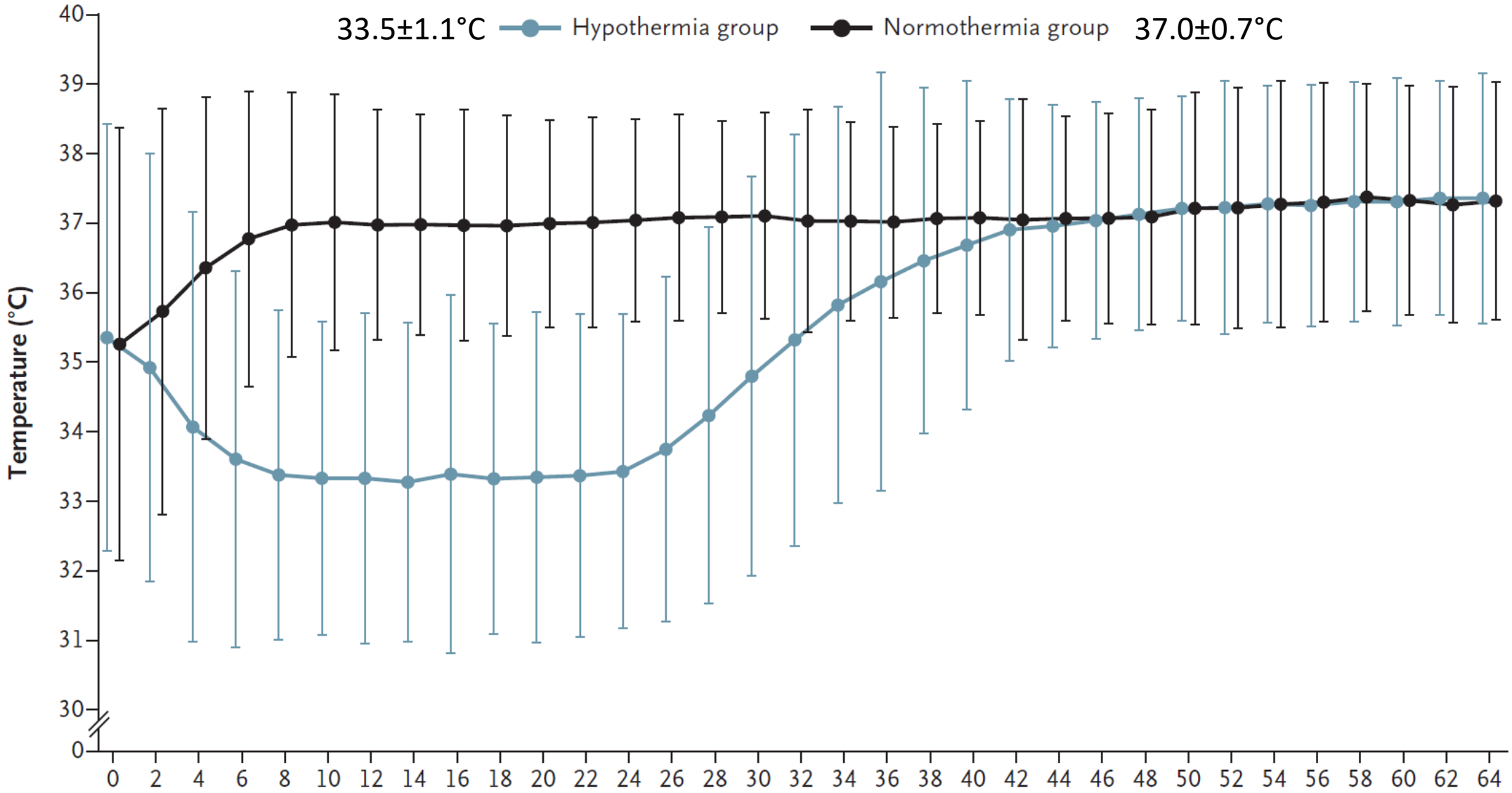
Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

J.-B. Lascarrou, H. Merdji, A. Le Gouge, G. Colin, G. Grillet, P. Girardie,

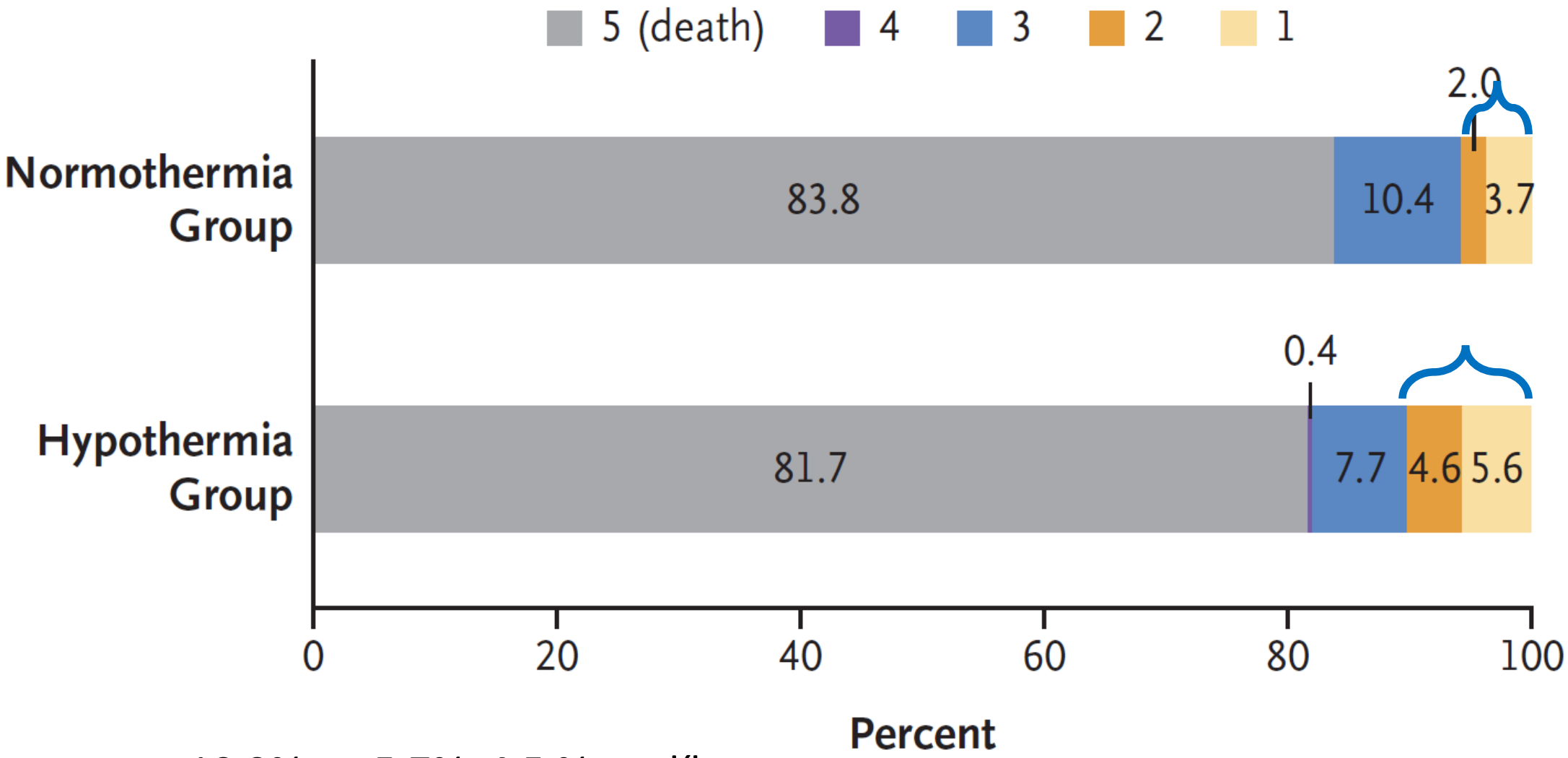
# Outcome

- Primární:
  - 90- přežití s příznivým neurologickým výstupem (CPC 1-2)
- Sekundární:
  - Mortalita
  - trvání UPV
  - LOS ICU a v nemocnici
  - Infekce
  - hematologické AE

DOI: 10.1056/NEJMoa1906661




DOI: 10.1056/NEJMoa1906661




10.2% vs. 5.7%; 4.5 % rozdíl
95% CI, 0.1-8.9; P = 0.04)

DOI: 10.1056/NEJMoa1906661

ORIGINAL ARTICLE

# Závěr

## Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

J.-B. Lascarrou, H. Merdji, A. Le Gouge, G. Colin, G. Grillet, P. Girardie,

In conclusion, among patients with coma who had been resuscitated from in-hospital or out-of-hospital cardiac arrest with nonshockable rhythm due to cardiac or noncardiac causes, the use of moderate therapeutic hypothermia at 33°C led to a higher percentage of patients who survived with a favorable neurologic outcome at day 90 than was observed with targeted normothermia.

DOI: 10.1056/NEJMoa1906661

ORIGINAL

# Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study

Mauro Oddo[1*], Claudio Sandroni[2], Giuseppe Citerio[3,4], John-Paul Miroz[1], Janneke Horn[5], Malin Rundgren[6], Alain Cariou[7,8], Jean-François Payen[9], Christian Storm[10], Pascal Stammet[11] and Fabio Silvio Taccone[12]

*Intensive Care Med (2018) 44:2102–2111*

ORIGINAL

# Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study

Mauro Oddo[1*], Claudio Sandroni[2], Giuseppe Citerio[3,4], John-Paul Miroz[1], Janneke Horn[5], Malin Rundgren[6], Alain Cariou[7,8], Jean-François Payen[9], Christian Storm[10], Pascal Stammet[11] and Fabio Silvio Taccone[12]

# Design

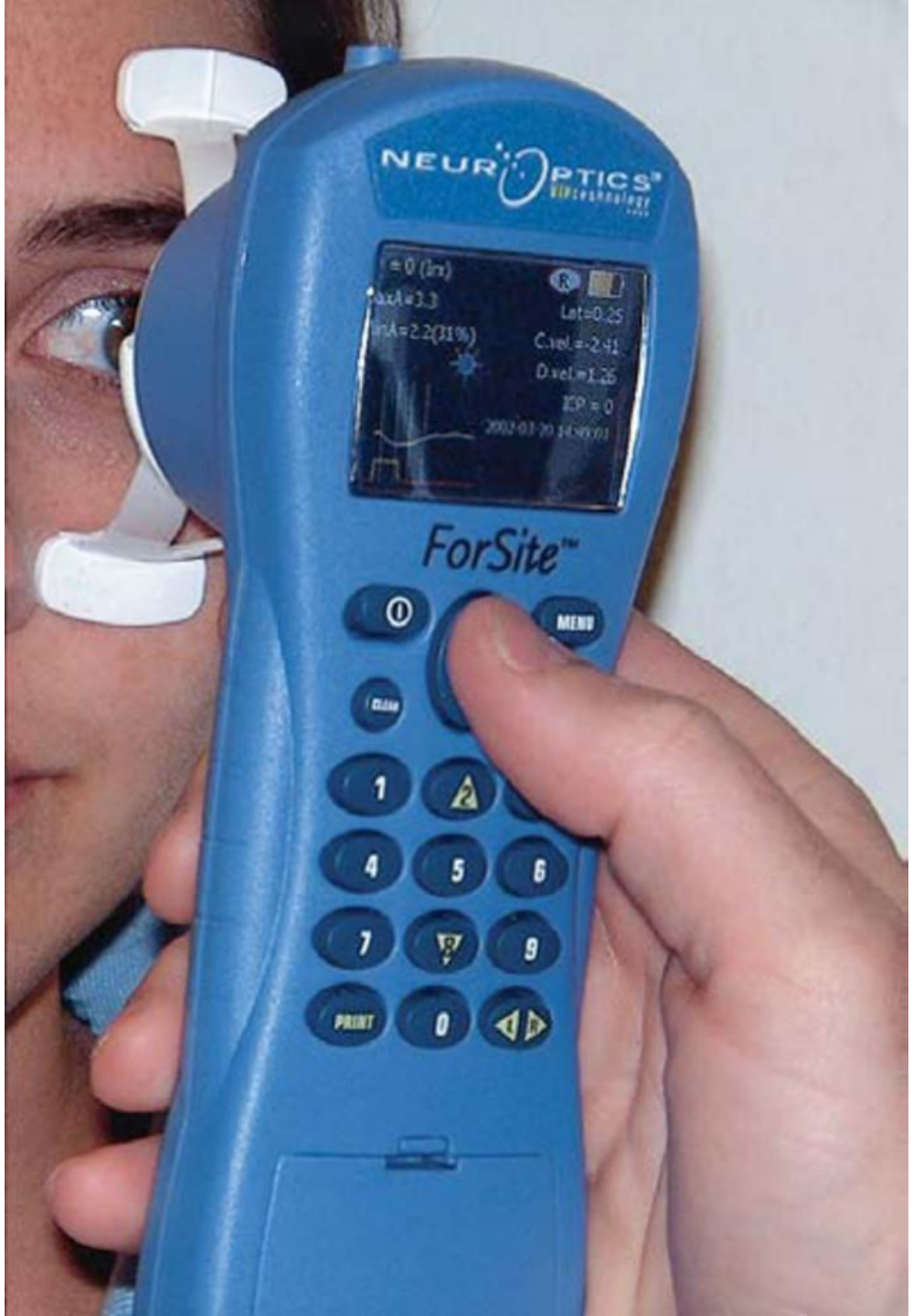
- Prospektivní multicentrická mezinárodní zaslepená prognostikační studie
- 456 komatózních pacienti >18 let po CA přijatí na ICU
- Hodnoceno denně mezi dny 1-3 po CA
- Cíl – zhodnotit úspěšnost NPi a srovnat se sPLR

*Intensive Care Med (2018) 44:2102–2111*

We recommend:

- Using the bilateral absence of both pupillary and corneal reflexes at 72 h or more from ROSC to predict poor outcome in comatose survivors from cardiac arrest, either TH-treated or non-TH-treated.

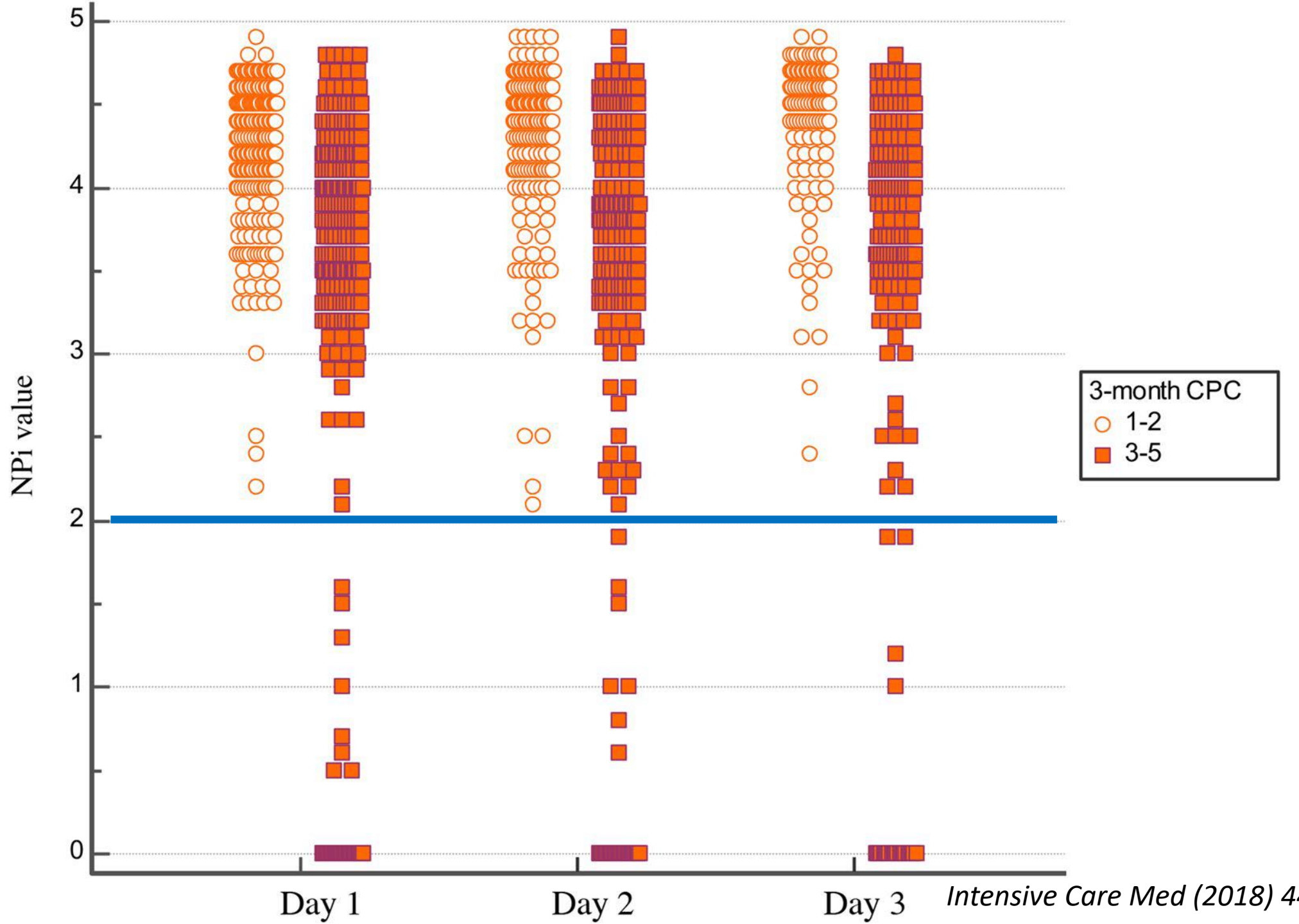
Intensive Care Med (2014) 40:1816–1831




# Pupilometrie

Založená na více měřitelných proměnných:
velikost, procento stažení, rychlost stažení,  rychlost dilatace, latence.
Neurological Pupil index (NPi):
škála 0-5
0 – areaktivní,
5 – nejvyšší reaktivita,
>3 – normální reaktivita

*Intensive Care Med (2018) 44:2102–2111*




*Intensive Care Med (2018) 44:2102–2111*

**Table 2 Specificity, sensitivity, positive predictive value, negative predictive value and false-positive rate for unfavorable outcome (CPC 3–5) of the different prognostic tests**

| Day after cardiac arrest | Sample size (*n*) | CPC 3–5 *n* (%) | Specificity % (95% CI) | Sensitivity % (95% CI) | Positive predictive value % (95% CI) | Negative predictive value % (95% CI) | False-positive rate % (95% CI) |
|---|---|---|---|---|---|---|---|
| Neurological pupil index (NPi) ≤ 2 | | | | | | | |
| Day 1–3 | 456 | 269 (59) | 100 (98–100) | 32 (27–38) | 100 (100–100) | 51 (49–53) | 0 (0–2) % |
| Day 1 | 450 | 264 (59) | 100 (98–100) | 22 (17–27) | 100 (100–100) | 47 (46–49) | 0 (0–2) % |
| Day 2 | 361 | 213 (59) | 100 (98–100) | 19 (14–25) | 100 (100–100) | 46 (45–48) | 0 (0–2) % |
| Day 3 | 271 | 166 (61) | 100 (97–100) | 17 (12–24) | 100 (100–100) | 43 (41–44) | 0 (0–3) % |
| Bilaterally absent standard pupillary light reflex (sPLR) | | | | | | | |
| Day 1 | 392 | 225 (57) | 90 (85–94) | 35 (29–42) | 83 (75–89) | 51 (48–54) | 10 (6–15) % |
| Day 2 | 278 | 163 (59) | 90 (84–95) | 29 (22–36) | 81 (70–89) | 47 (44–50) | 10 (5–16) % |
| Day 3 | 206 | 128 (62) | 94 (86–98) | 18 (12–26) | 82 (65–92) | 41 (39–43) | 6 (2–14) % |
| Bilaterally absent somatosensory evoked potentials (N20 wave) | | | | | | | |
| Day 2–3 | 188 | 133 (71) | 100 (94–100) | 48 (39–57) | 100 (100–100) | 44 (40–48) | 0 (0–6) % |
| Combination of NPi ≤ 2 and bilaterally absent somatosensory evoked potentials | | | | | | | |
| Day 2–3 | 188 | 133 (71) | 100 (94–100) | 58 (49–66) | 100 (100–100) | 55 (50–59) | 0 (0–6) % |

*Intensive Care Med (2018) 44:2102–2111*

Our main findings are that a NPi $\leq 2$, performed at any time between day 1 and day 3 following hospital admission, was 100% specific to predict an unfavorable 3-month neurological outcome and provided greater prognostic performance than standard manual pupillary light reactivity. Our data further suggest that using a prognostic approach that combines the NPi with somatosensory evoked potentials improved the sensitivity to predict an unfavorable outcome in patients with cardiac arrest, while providing equal 100% specificity. Future

*Intensive Care Med (2018) 44:2102–2111*

# Ventilace

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2019 VOL. 380 NO. 9

# Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

Jonathan D. Casey, M.D., David R. Janz, M.D., Derek W. Russell, M.D., Derek J. Vonderhaar, M.D., Aaron M. Joffe, D.O., Kevin M. Dischert, M.D., Ryan M. Brown, M.D., Aline N. Zouk, M.D., Swati Gulati, M.B., B.S., Brent E. Heideman, M.D., Michael G. Lester, M.D., Alexandra H. Toporek, M.D., Itay Bentov, M.D., Ph.D., Wesley H. Self, M.D., Todd W. Rice, M.D., and Matthew W. Semler, M.D., for the PreVent Investigators and the Pragmatic Critical Care Research Group*

Pre-Vent

N Engl J Med 2019;380:811-21.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2019 VOL. 380 NO. 9

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

# Design

- multicenter, parallel-group, nezaslepená, pragmatická, randomizovaná studie
- 401 pacientů randomizovaných na ventilaci samorozpínacím vakem od indukce do intubace vs. žádná ventilace

N Engl J Med 2019;380:811-21.

ORIGINAL ARTICLE

# Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

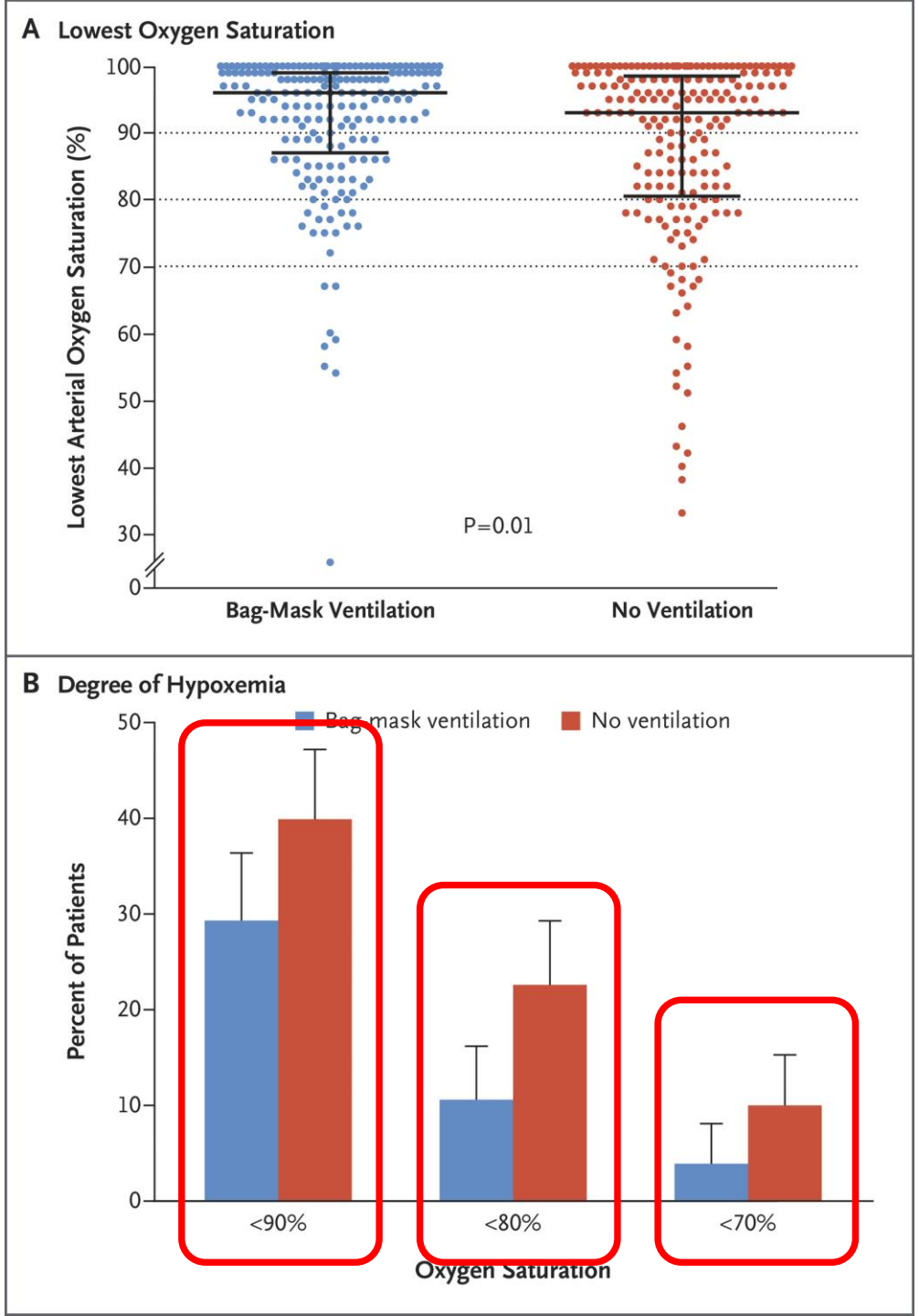
# Outcome

- Primární : nejnižší $SpO_2$ od indukce do 2 minut po intubaci
- Sekundární:
  - Incidence těžké hypoxémie (<80%)
- Procedurální outcome:
  - $SpO_2$, $fiO_2$, PEEP 24 hodin po intubaci
  - Detekce aspirace/nové infiltrace na Rtg

N Engl J Med 2019;380:811-21.

oxygen flow rates of at least 15 liters per minute, a valve attached to the expiratory port of the bag-mask device to generate a positive end-expiratory pressure of 5 to 10 cm of water, an oropharyngeal airway, a two-handed mask seal performed by the intubating clinician with a head-tilt and chin-lift maneuver, and ventilation at 10 breaths per minute with the smallest volume required to generate a visible chest rise.[21] Failure to admin-

N Engl J Med 2019;380:811-21.




N Engl J Med 2019;380:811-21.

**Table 3. Outcomes of Tracheal Intubation.**

| Outcome | Bag-Mask Ventilation (N = 199) | No Ventilation (N = 202) | Relative Risk or Mean Difference (95% CI) |
|---|---|---|---|
| Primary: median lowest oxygen saturation (IQR) — %* | 96 (87–99) | 93 (81–99) | 3.9 (1.4 to 6.5)† |
| Secondary: lowest oxygen saturation of <80% — no./total no. (%) | 21/193 (10.9) | 45/197 (22.8) | 0.48 (0.30 to 0.77) |
| Exploratory oxygen-saturation outcomes | | | |
| Lowest oxygen saturation of <90% — no./total no. (%) | 57/193 (29.5) | 79/197 (40.1) | 0.74 (0.56 to 0.97) |
| Lowest oxygen saturation of <70% — no./total no. (%)‡ | 8/193 (4.1) | 20/197 (10.2) | 0.41 (0.18 to 0.90) |
| Median decrease in oxygen saturation (IQR) — percentage points | 1 (0–7) | 5 (0–14) | −4.5 (−6.8 to −2.2)† |
| Exploratory safety outcomes | | | |
| Operator-reported aspiration — no. (%) | 5 (2.5) | 8 (4.0) | 0.63 (0.21 to 1.91) |
| New opacity on chest radiography — no./total no. (%) | 31/189 (16.4) | 29/196 (14.8) | 1.11 (0.70 to 1.77) |
| New pneumothorax — no./total no. (%) | 2/189 (1.1) | 6/196 (3.1) | 0.34 (0.07 to 1.66) |
| New vasopressor after induction — no./total no. (%) | 39/196 (19.9) | 46/199 (23.1) | 0.86 (0.59 to 1.26) |
| New systolic blood pressure of <65 mm Hg — no./total no. (%) | 8/195 (4.1) | 17/197 (8.6) | 0.48 (0.21 to 1.08) |
| Cardiac arrest within 1 hr after intubation — no. (%) | 2 (1.0) | 4 (2.0) | 0.51 (0.09 to 2.74) |
| Exploratory clinical outcomes | | | |
| Median no. of ventilator-free days (IQR) | 19 (0–25) | 18 (0–25) | 0.6 (−1.7 to 2.9)† |
| Median no. of days outside intensive care unit (IQR) | 16 (0–22) | 14 (0–22) | 0.8 (−1.3 to 2.9)† |
| Death before hospital discharge — no. (%) | 71 (35.7) | 72 (35.6) | 1.00 (0.77 to 1.30) |

N Engl J Med 2019;380:811-21.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2019 VOL. 380 NO. 9

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

# Závěr

- Pacienti ve skupině intubovaných s ventilací mezi indukcí a intubací měli vyšší $SpO_2$ a nižší incidenci těžké desaturace než pacienti, kteří nebyli ventilováni
- Ventilace maskou nevedlo ke zvýšení incidence aspirace a komplikací

N Engl J Med 2019;380:811-21.

ORIGINAL

# Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome

Zhongheng Zhang[1*], Bin Zheng[2], Nan Liu[3,4], Huiqing Ge[5] and Yucai Hong[1]

*Intensive Care Med (2019) 45:856–864*

ORIGINAL

# Ventilator-related causes of lung injury: the mechanical power

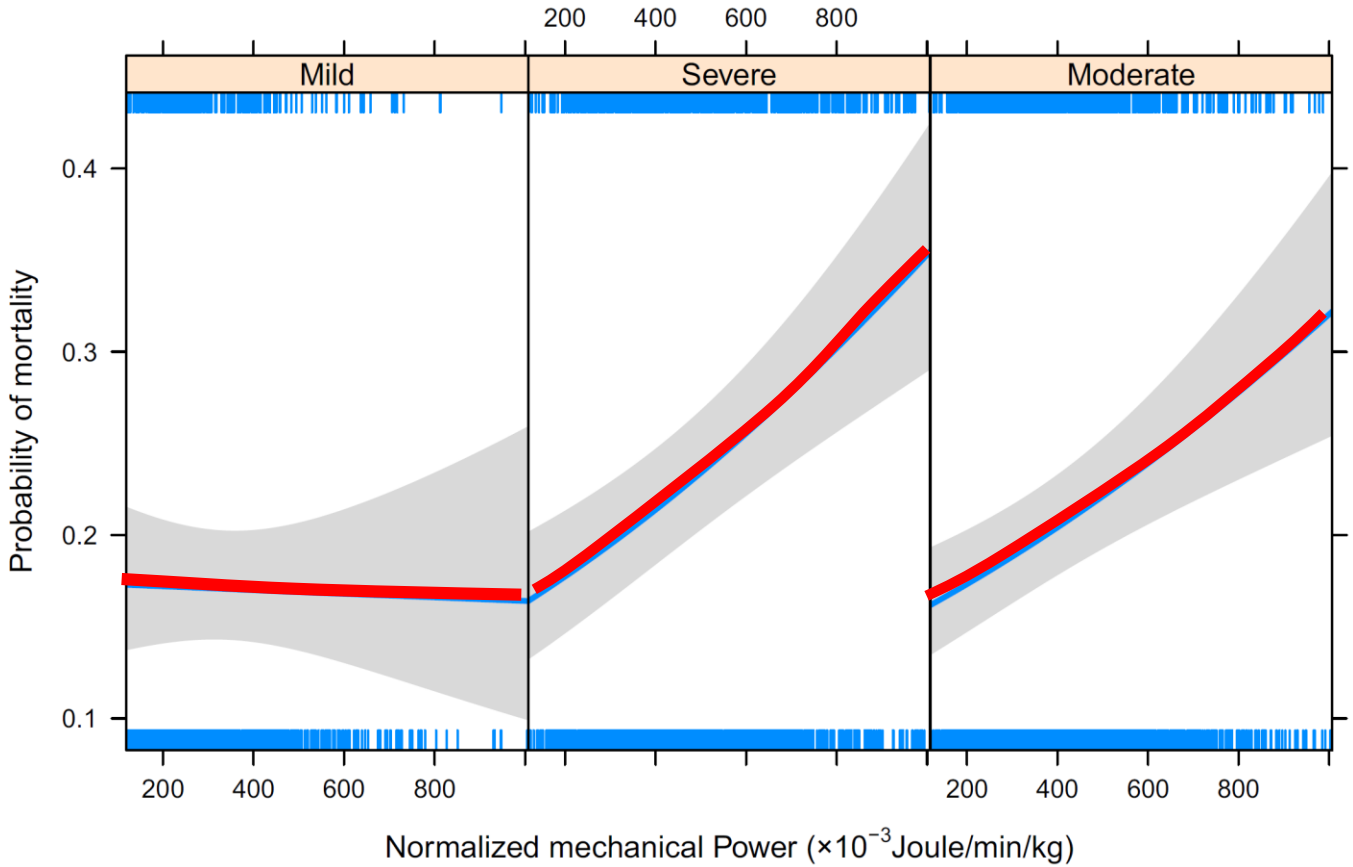
L. Gattinoni[1*], T. Tonetti[1], M. Cressoni[2], P. Cadringher[3], P. Herrmann[1], O. Moerer[1], A. Protti[3], M. Gotti[2], C. Chiurazzi[2], E. Carlesso[2], D. Chiumello[4] and M. Quintel[1]

$$\text{Power}_{rs} = \boxed{RR} \cdot \left\{ \boxed{\Delta V^2} \cdot \left[ \frac{1}{2} \cdot \boxed{EL_{rs}} + \boxed{RR} \cdot \frac{(1 + I:E)}{60 \cdot I:E} \cdot \boxed{R_{aw}} \right] + \boxed{\Delta V} \cdot \boxed{PEEP} \right\}$$

*Intensive Care Med (2016) 42:1567–1575*

# Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome

Zhongheng Zhang[1*], Bin Zheng[2], Nan Liu[3,4], Huiqing Ge[5] and Yucai Hong[1]




| Ventilator parameters | AUROC | Lower limit of 95% CI | Upper limit of 95% CI |
|---|---|---|---|
| Tidal volume (mL) | 0.744 | 0.713 | 0.775 |
| Tidal volume normalized to PBW (mL/kg) | 0.746 | 0.715 | 0.777 |
| Respiratory rate (/min) | 0.743 | 0.713 | 0.774 |
| PEEP ($cmH_2O$) | 0.744 | 0.713 | 0.775 |
| Plateau pressure ($cmH_2O$) | 0.747 | 0.716 | 0.778 |
| PIP ($cmH_2O$) | 0.746 | 0.715 | 0.777 |
| Driving pressure ($cmH_2O$) | 0.743 | 0.712 | 0.774 |
| MP (J/min) | 0.747 | 0.717 | 0.778 |
| norMP ($10^{-3}$ J/min/kg) | 0.751 | 0.720 | 0.781 |
| MP normalized to compliance | 0.753 | 0.722 | 0.783 |
| Gradient boosting machine | 0.748 | 0.717 | 0.779 |

*Intensive Care Med (2019) 45:856–864*

ORIGINAL

# Structural differences in the diaphragm of patients following controlled vs assisted and spontaneous mechanical ventilation

J. Marin-Corral[1,2*], I. Dot[1,2], M. Boguña[2,3], L. Cecchini[4], A. Zapatero[1,2], M. P. Gracia[1,2], S. Pascual-Guardia[5,6], C. Vilà[1,2], A. Castellví[1,2], P. Pérez-Terán[1,2], J. Gea[5,6,7] and J. R. Masclans[1,2,8]

*Intensive Care Med (2019) 45:488–500*

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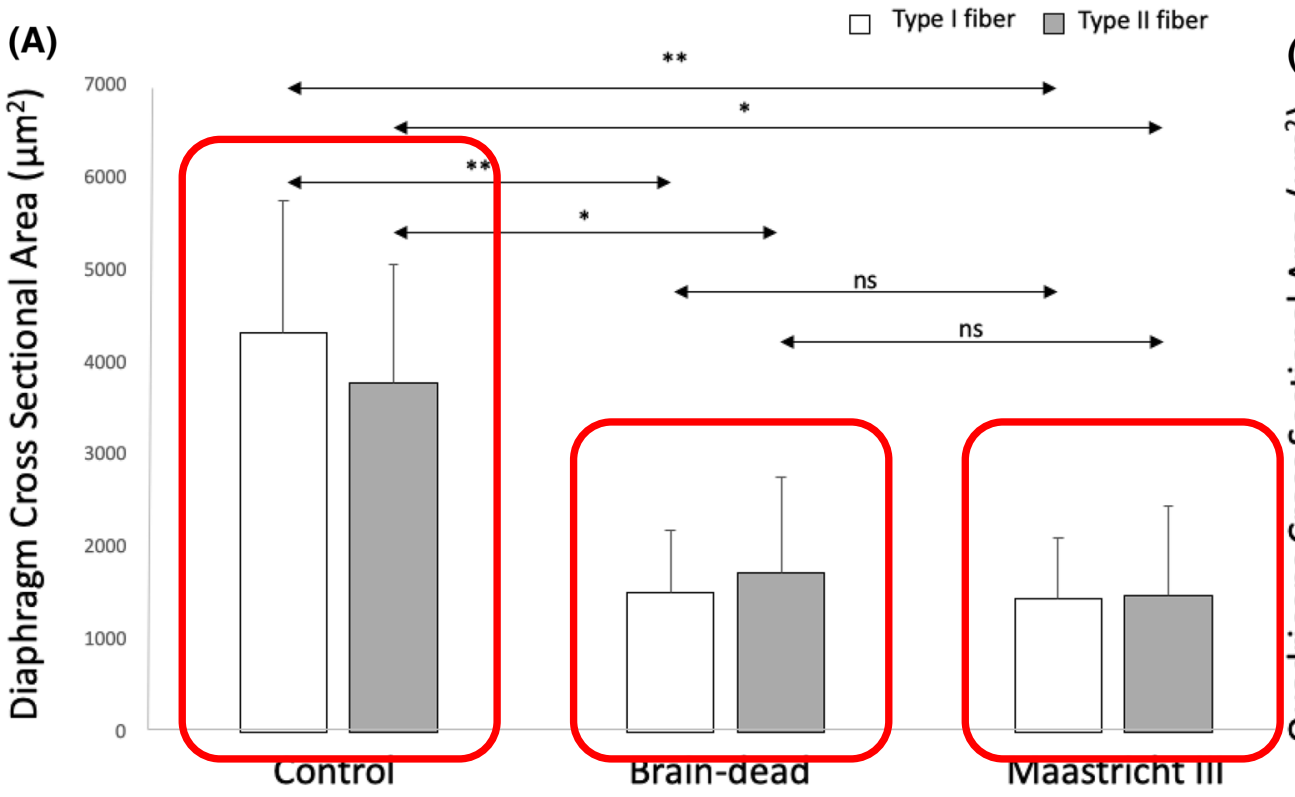
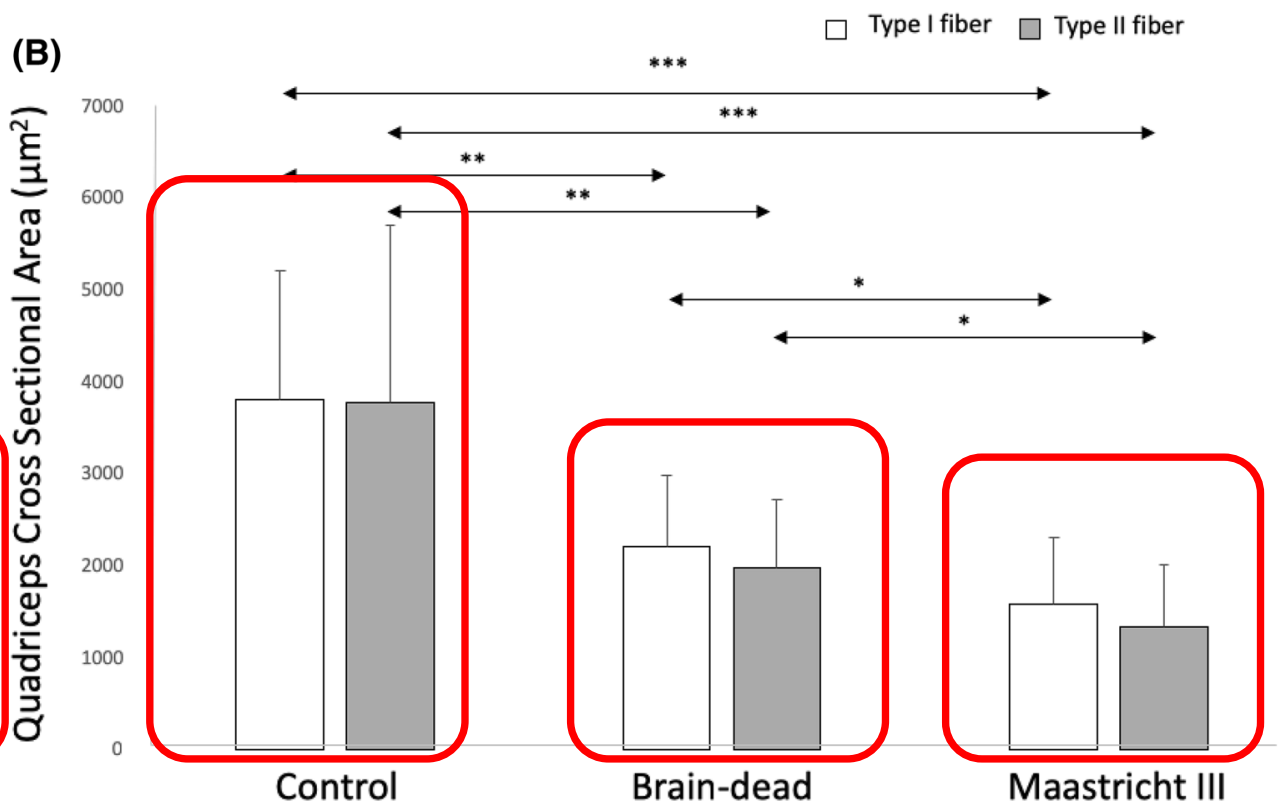
# Design

- Prospektivní observační studie
- Srovnání biopsií 16 MSIII dárců, 14 dárců s mozkovou smrtí a 5 kontrolních subjektů (chirurgičtí pacienti)
- Srovnání průřezu MHCH I a II
- Stanovení vlivu doby bez stimulace bránice (<100 dní vs. >100 dní) na rozvoj VIDD

*Intensive Care Med (2019) 45:488–500*

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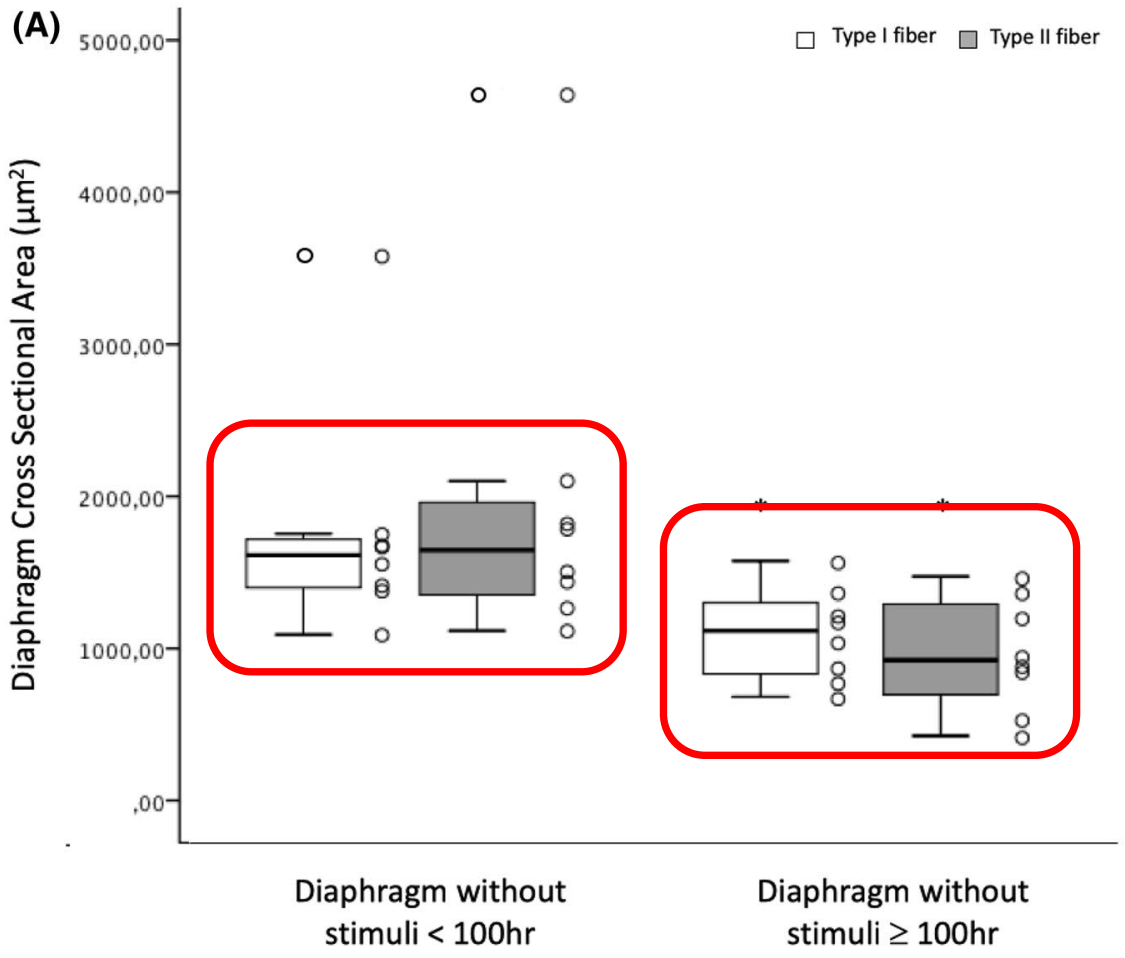


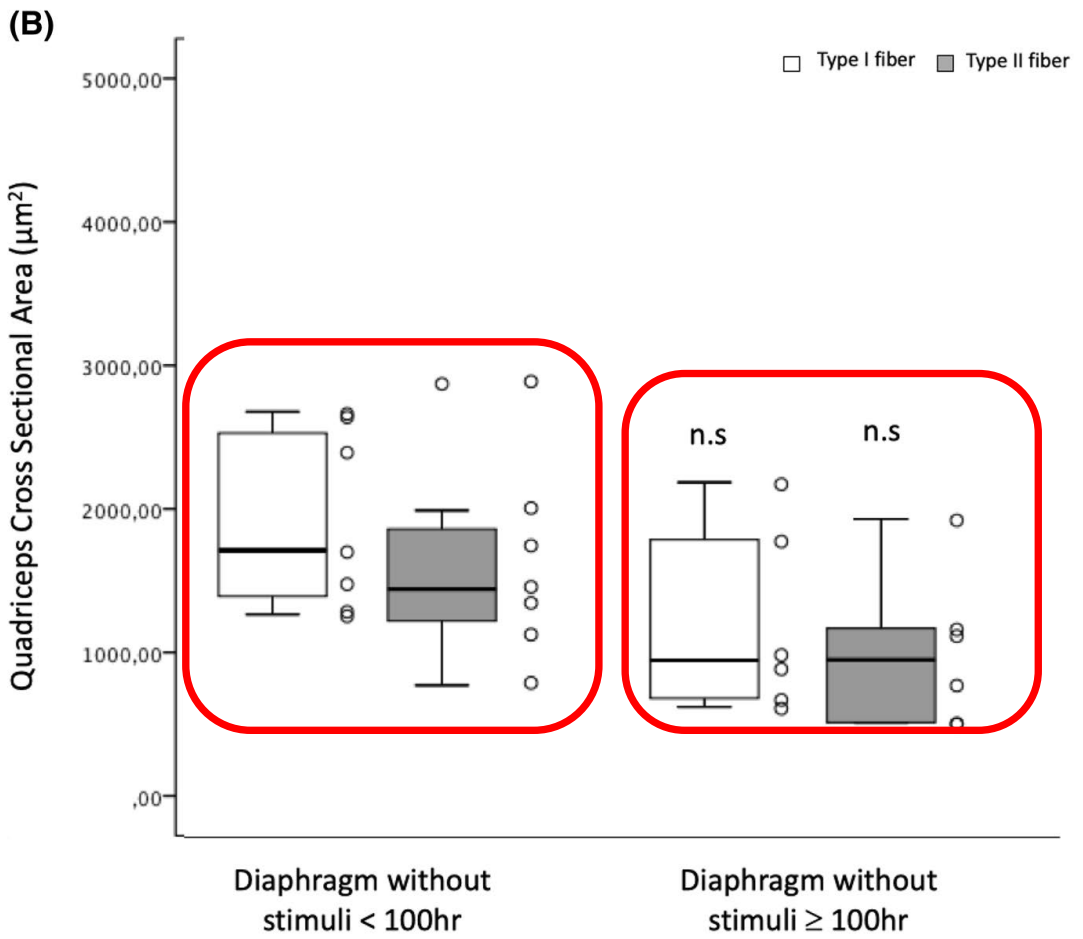


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- První humánní důkaz o vlivu doby bez stimulace na VIDD
- Inaktivita bránice po dobu CMV má vliv na rozvoj VIDD

*Intensive Care Med (2019) 45:488–500*

# AKI

ORIGINAL ARTICLE

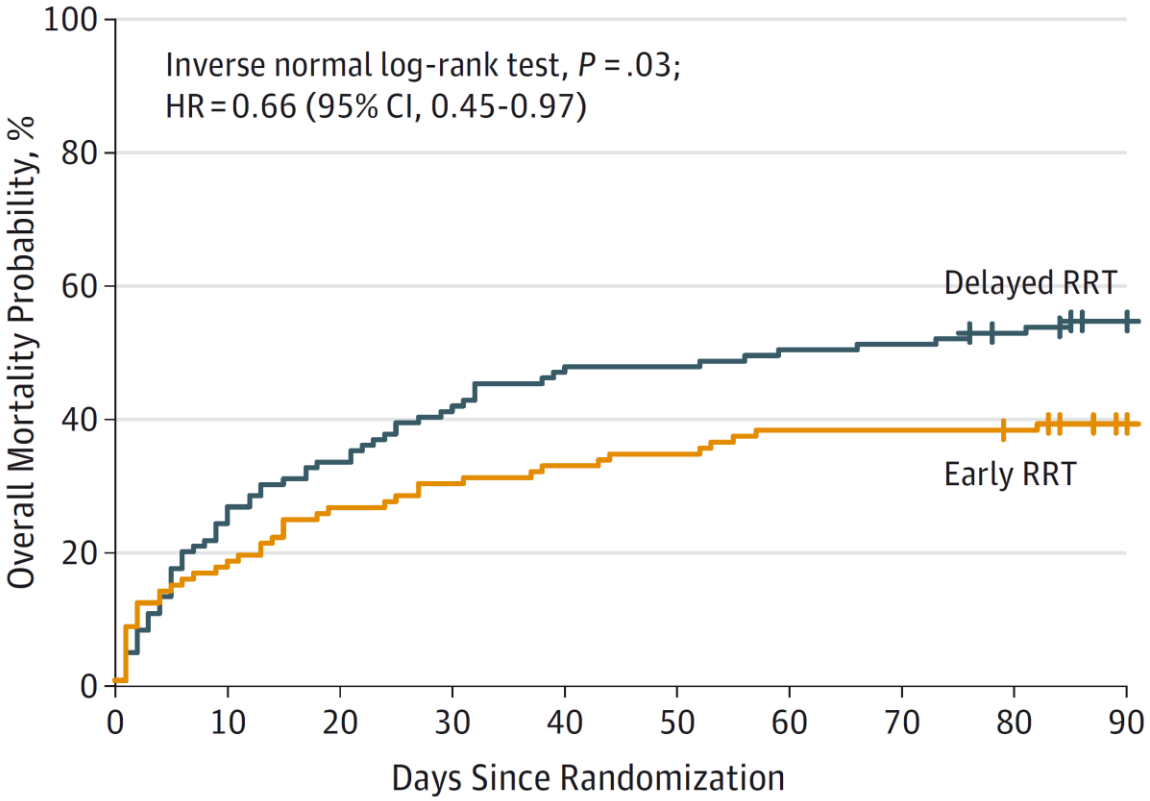
# Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

S.D. Barbar, R. Clere-Jehl, A. Bourredjem, R. Hernu, F. Montini, R. Bruyère, C. Lebert, J. Bohé, J. Badie, J.-P. Eraldi, J.-P. Rigaud, B. Levy, S. Siami, G. Louis, L. Bouadma, J.-M. Constantin, E. Mercier, K. Klouche, D. du Cheyron, G. Piton, D. Annane, S. Jaber, T. van der Linden, G. Blasco, J.-P. Mira, C. Schwebel, L. Chimot, P. Guiot, M.-A. Nay, F. Meziani, J. Helms, C. Roger, B. Louart, R. Trusson, A. Dargent, C. Binquet, and J.-P. Quenot, for the IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network*

IDEAL-ICU

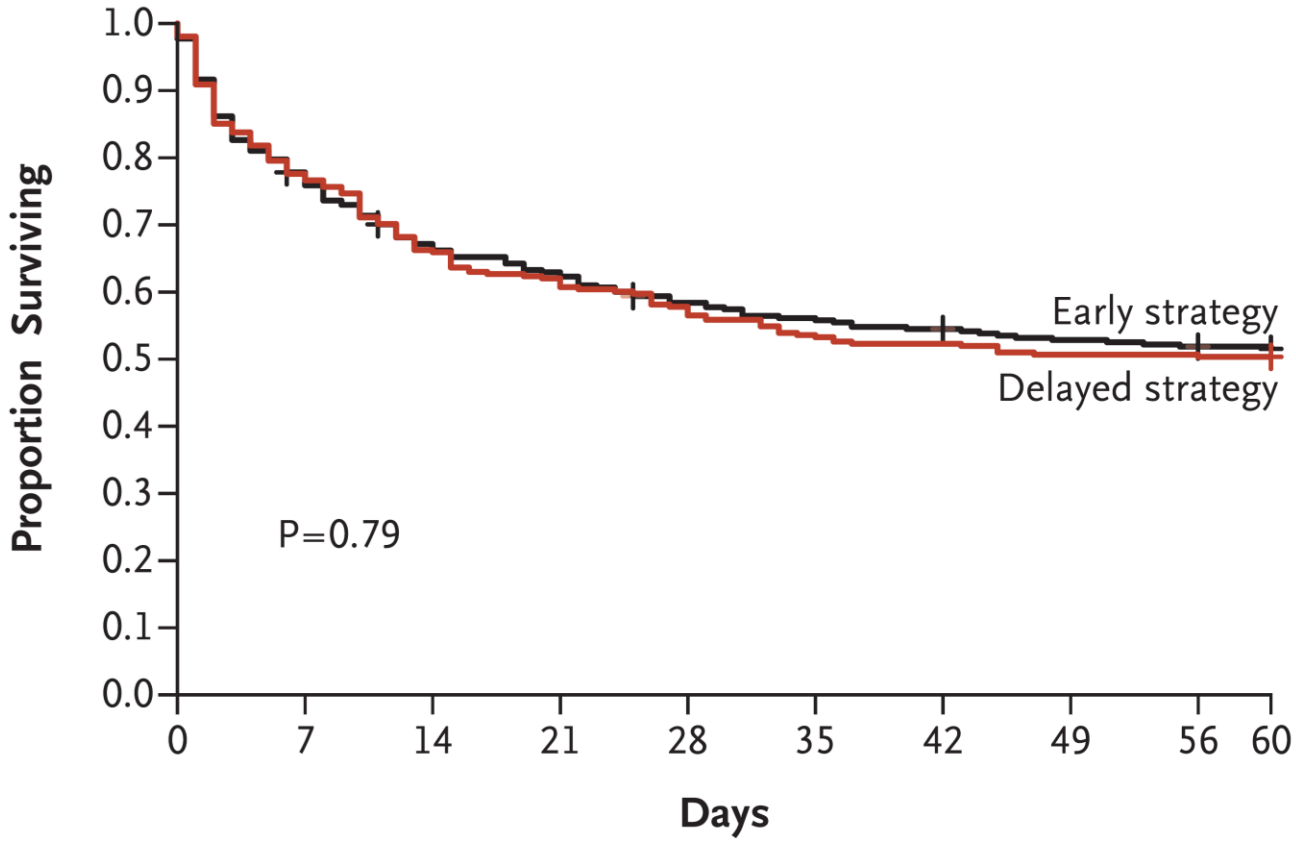
N Engl J Med 2018;379:1431-42.

# ELAIN

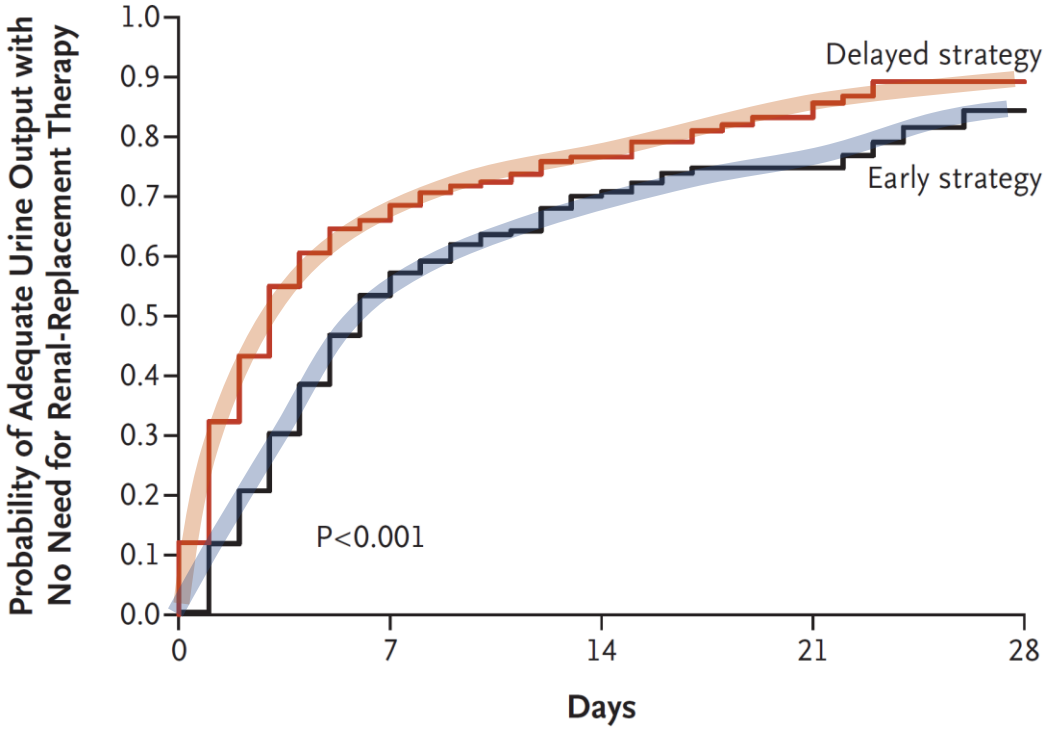


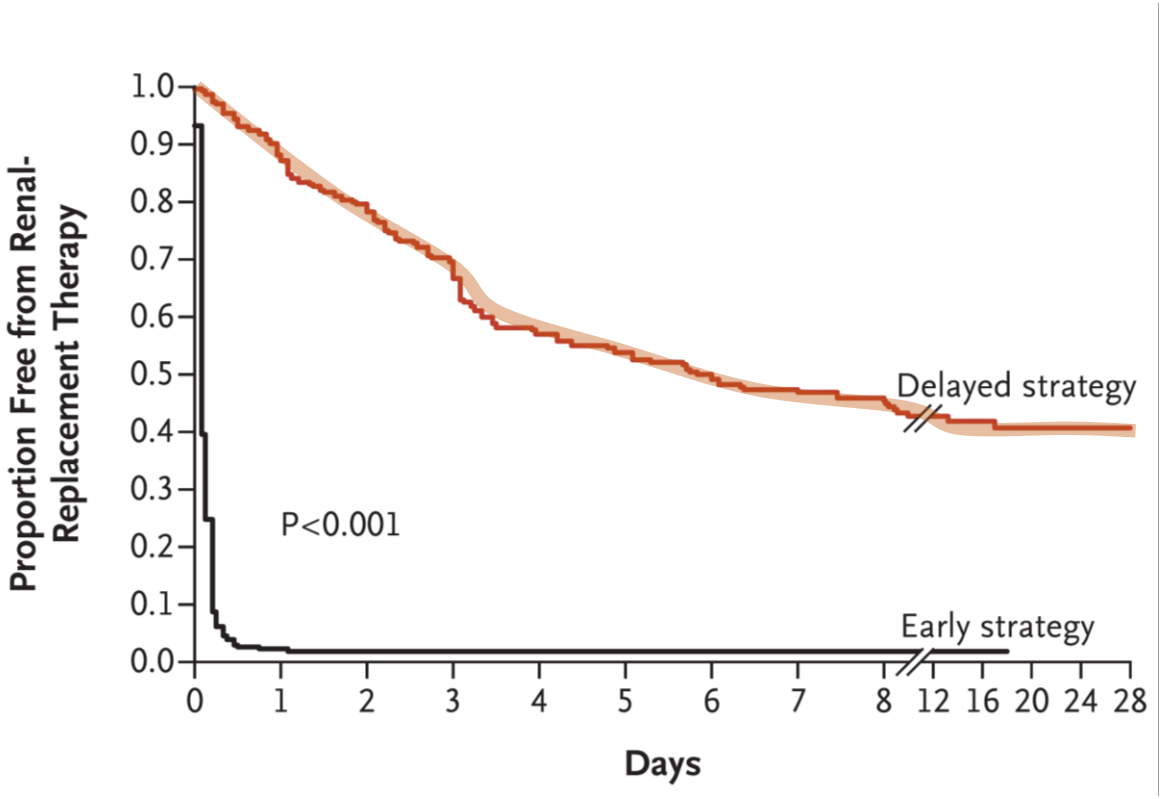

*JAMA*. 2016;315(20):2190-2199

# AKIKI




N Engl J Med 2016;375:122-33.




N Engl J Med 2016;375:122-33.

AKIKI

ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

# Design

- Multicentrická randomizovaná nezaslepená studie
- RIFLE-F, septický šok < 48 hodin
- RRT <12 hodin vs. 48 hodin
- 488 pacientů v sepsi s AKI RIFLE F

N Engl J Med 2018;379:1431-42.

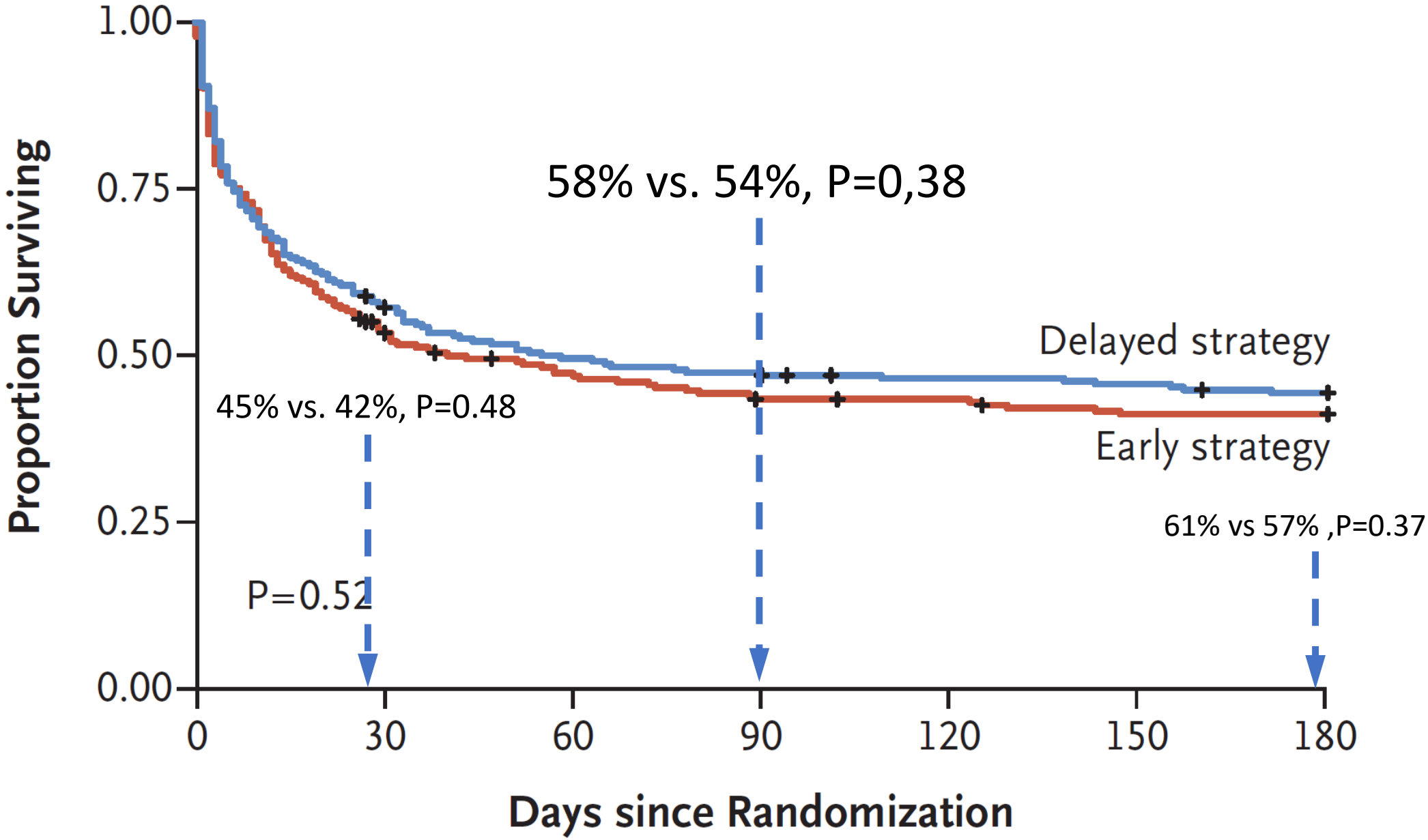
ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

# Outcome

- Primární: 90 – denní mortalita
- Sekundární:
  - 180 – denní a 28 – denní mortalita
  - ICU, hospital LOS
  - AE celkově/7 dní
  - BT za 7 dní
  - Potřeba emergentní RTT ve skupině 48 hodin
  - Mortalita u pacientů ve skupině >48 hodin, s kritérii pro emergentní RRT
  - Závislost na RRT při propuštění z nemocnice
- Power analýza při rozdílu mortality 45 vs. 55% 864 pacientů

N Engl J Med 2018;379:1431-42.




N Engl J Med 2018;379:1431-42.

**Table 2. Primary and Secondary Outcomes.***

| Variable | Early Strategy (N = 246) | Delayed Strategy (N = 242) | P Value |
|---|---|---|---|
| **Primary outcome** | | | |
| Death at 90 days — no./total no. (%) | 138/239 (58) | 128/238 (54) | 0.38 |
| **Secondary outcomes** | | | |
| Death at 28 days — no. (%) | 111 (45) | 102 (42) | 0.48 |
| Death at 180 days — no./total no. (%) | 143/236 (61) | 134/235 (57) | 0.37 |
| Median time from diagnosis of failure-stage acute kidney injury to initiation of renal-replacement therapy (IQR) — hr† | 7.6 (4.4–11.5) | 51.5 (34.6–59.5) | <0.001 |
| Patients who received renal-replacement therapy — no. (%) | 239 (97) | 149 (62) | <0.001 |
| Patients in the delayed-strategy group who received emergency renal-replacement therapy before 48 hr, according to criterion — no. (%)‡ | | 41 (17) | |
| Metabolic acidosis | | | |
| No. of patients (%) | | 20 (8) | |
| Median pH (IQR) | | 7.10 (7.06–7.13) | |
| Hyperkalemia | | | |
| No. of patients (%) | | 9 (4) | |
| Median potassium level (IQR) — mmol/liter | | 7.0 (6.7–7.3) | |
| Fluid overload — no. (%) | | 6 (2) | |
| Other criterion — no. (%)§ | | 6 (2) | |
| Median days of renal-replacement therapy (IQR) | 4 (2–8) | 2 (0–6) | <0.001 |
| Median days free of renal-replacement therapy (IQR)¶ | 12 (1–25) | 16 (2–28) | 0.006 |

N Engl J Med 2018;379:1431-42.

| | | | |
|---|---|---|---|
| Median days free of mechanical ventilation (IQR)¶ | 2 (0–19) | 3 (0–21) | 0.19 |
| Median days free of vasopressors (IQR)¶ | 16 (0–25) | 17 (0–25) | 0.87 |
| Median length of ICU stay (IQR) — days | 11 (4–19) | 10 (5–19) | 0.91 |
| Survivors | 12 (8–21) | 12 (8–21) | 0.88 |
| Nonsurvivors | 5 (2–15) | 6 (3–14) | 0.64 |
| Median length of hospital stay (IQR) — days | 23 (10–40) | 23 (10–44) | 0.34 |
| Survivors | 22.0 (9.0–38.0) | 21.0 (10.0–42.5) | 0.53 |
| Nonsurvivors | 25 (15–53) | 42 (33–56) | 0.08 |
| SOFA score without renal component‖ | | | |
| Day 1 | 9.3±3.5 | 9.3±3.2 | 0.84 |
| Day 2 | 8.6±3.8 | 8.4±3.9 | 0.57 |
| Day 3 | 8.0±4.0 | 7.8±4.1 | 0.64 |
| Day 7 | 5.9±3.8 | 6.3±3.9 | 0.30 |
| Fluid balance — ml | | | |
| Cumulative fluid balance after day 2 | 3737±3925 | 3437±3371 | 0.40 |
| Cumulative fluid balance at day 7 | 5570±8761 | 5878±7472 | 0.75 |
| Receipt of diuretics from day 0 to 7 | | | |
| No. of patients (%) | 121 (49) | 124 (51) | 0.65 |
| Median cumulative dose of furosemide from day 0 to 7 (IQR) — mg | 215 (65–760) | 295 (80–1160) | 0.18 |
| Dependence on renal-replacement therapy among survivors — no./total no. (%) | | | |
| Day 28 | 17/134 (13) | 17/140 (12) | 0.89 |
| Day 90 | 2/101 (2) | 3/110 (3) | 1.00 |

N Engl J Med 2018;379:1431-42.

# Tekutinová bilance

**Table S9. Fluid Balance in the First 7 Days after Randomization**

| | EARLY RRT N= 246 | | | | DELAYED RRT n=242 | | | | p Value* |
|---|---|---|---|---|---|---|---|---|---|
| | Fluid intake | Urinary output | RRT ultrafiltration | Net fluid balance | Fluid intake | Urinary output | RRT ultrafiltration | Net fluid balance | |
| Day 1 (ml) | 3024 (2261; 3977) | 400 (100; 1088) | 0 (0; 500) | 1812 (850; 3450) | 2941 (2135; 3827) | 700 (157; 1480) | 0 (0; 0) | 1754 (750; 2948) | 0.3513 |
| Day 2 (ml) | 2791 (1963; 3470) | 570 (121; 1450) | 0 (0; 1300) | 1179 (180; 2263) | 2802 (2121; 3599) | 1043 (200; 2052) | 0 (0; 420) | 1214 (28; 2190) | 0.9888 |
| Day 3 (ml) | 2490 (1680; 3240) | 646 (98; 1720) | 0 (0; 1200) | 720 (-575; 1823) | 2509 (2010; 3180) | 930 (200; 1800) | 0 (0; 1153) | 949 (-727; 1768) | 0.9738 |
| Day 4 (ml) | 2420 (1835; 3344) | 1253 (200; 2335) | 0 (0; 1013) | 529 (-1095; 1481) | 2550 (1900; 3168) | 1250 (210; 2300) | 0 (0; 1770) | 295 (-944; 1290) | 0.487 |
| Day 5 (ml) | 2450 (1918; 3200) | 1532 (345; 2544) | 0 (0; 1000) | 37 (-940; 1200) | 2546 (1830; 3182) | 1600 (125; 2500) | 0 (0; 1500) | 0 (-1320; 1361) | 0.7507 |
| Day 6 (ml) | 2454 (1720; 3194) | 1400 (400; 2753) | 0 (0; 1365) | -192 (-1371; 1337) | 2499 (1845; 3036) | 1585 (413; 2832) | 0 (0; 1938) | 100 (-1051; 1033) | 0.7631 |
| Day 7 (ml) | 2382 (1579; 3180) | 1700 (505; 3001) | 0 (0; 0) | -220 (-1324; 1050) | 2414 (1850; 3041) | 1500 (415; 2300) | 0 (0; 1000) | 268 (-1031; 1360) | 0.2189 |
| Day 1-Day 7 Sum (ml) | 19035 (15615; 22392) | 10090 (4121; 15500) | 4094 (0; 9665) | 2275 (-2770; 8820) | 18479 (16137; 21831) | 11050 (4540; 15585) | 1188 (0; 9285) | 3678 (-585; 8311) | 0.4784 |

N Engl J Med 2018;379:1431-42.

ORIGINAL ARTICLE

# Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

Časná náhrada renálních funkcí u pacientů v septickém šoku s těžkým AKI, bez anurie a přetížení tekutinami a bez akutní indikace k RRT nevede ke snížení mortality

N Engl J Med 2018;379:1431-42.

# Nutrice

ORIGINAL ARTICLE

# Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

TARGET

N Engl J Med 2018;379:1823-34.

ORIGINAL ARTICLE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

# Design

- Multicentrická randomizovaná dvojitě zaslepená pragmatická studie
- 46 ICU ANZ
- 3914 pacientů >18 let, UPV, <12 hodin podávaná EN
- Power analýza – 3774 pacientů pro 80% pravděpodobnost detekce 3.8 – 4,8% rozdíl v 90 – denní mortalitě

N Engl J Med 2018;379:1823-34.

ORIGINAL ARTICLE

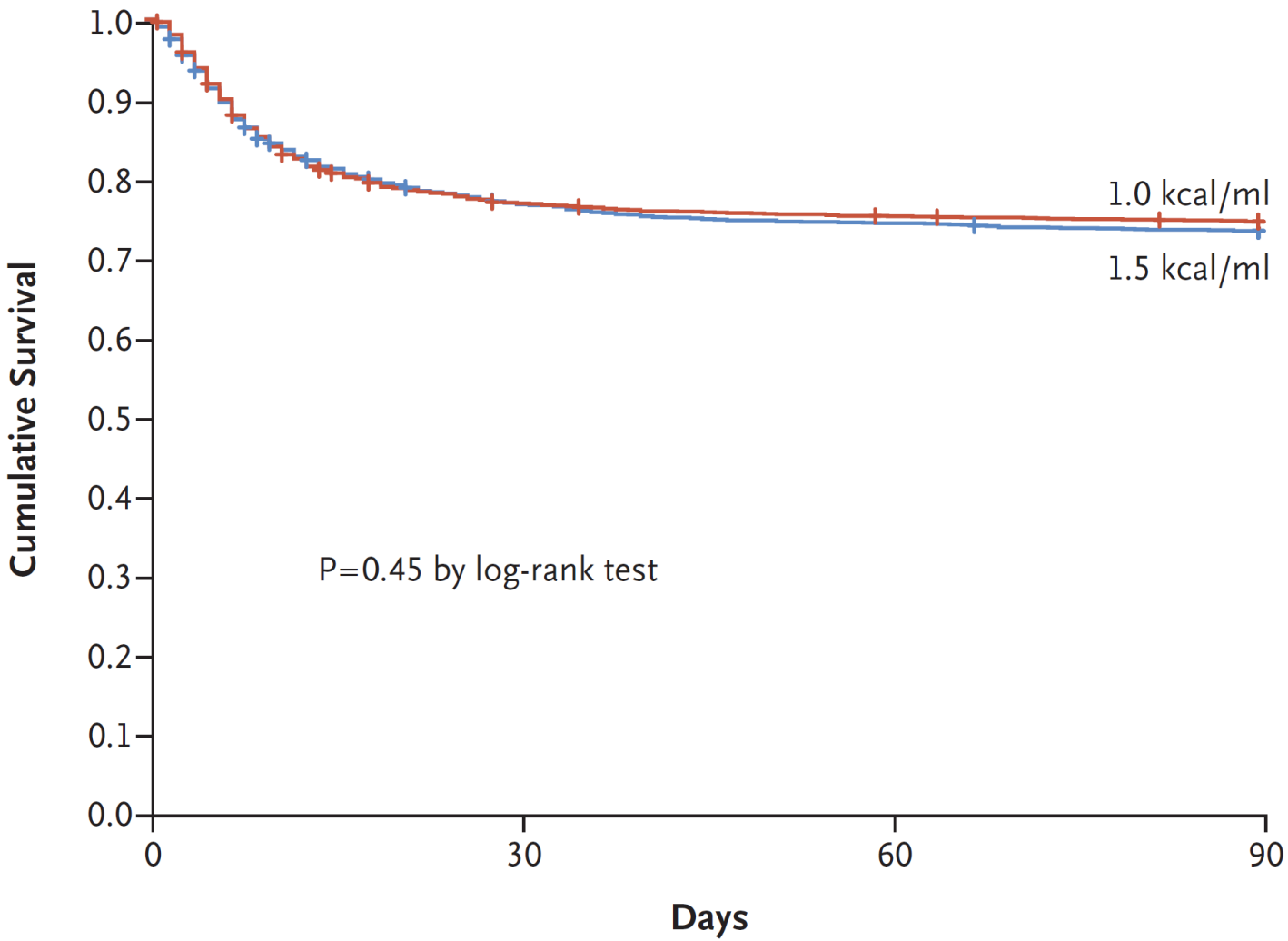
# Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

# Outcome

- Primární: 90 – denní mortalita
- Sekundární:
  - Čas přežití
  - 28 – denní mortalita, nemocniční mortalita
  - Dny bez orgánové podpory před dnem 28
  - % pacientů na UPV, s vasopresory, RRT
  - ATB, pozitivní hemokultury
- Podskupiny:
  - Trauma, sepse, trauma, sepsis, neurologické onemocnění, interní/chirurgičtí pacienti, kvintily AR mortality, BMI (<18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30.0).

N Engl J Med 2018;379:1823-34.




N Engl J Med 2018;379:1823-34.

**Table 3. Outcomes and Adverse Events.**

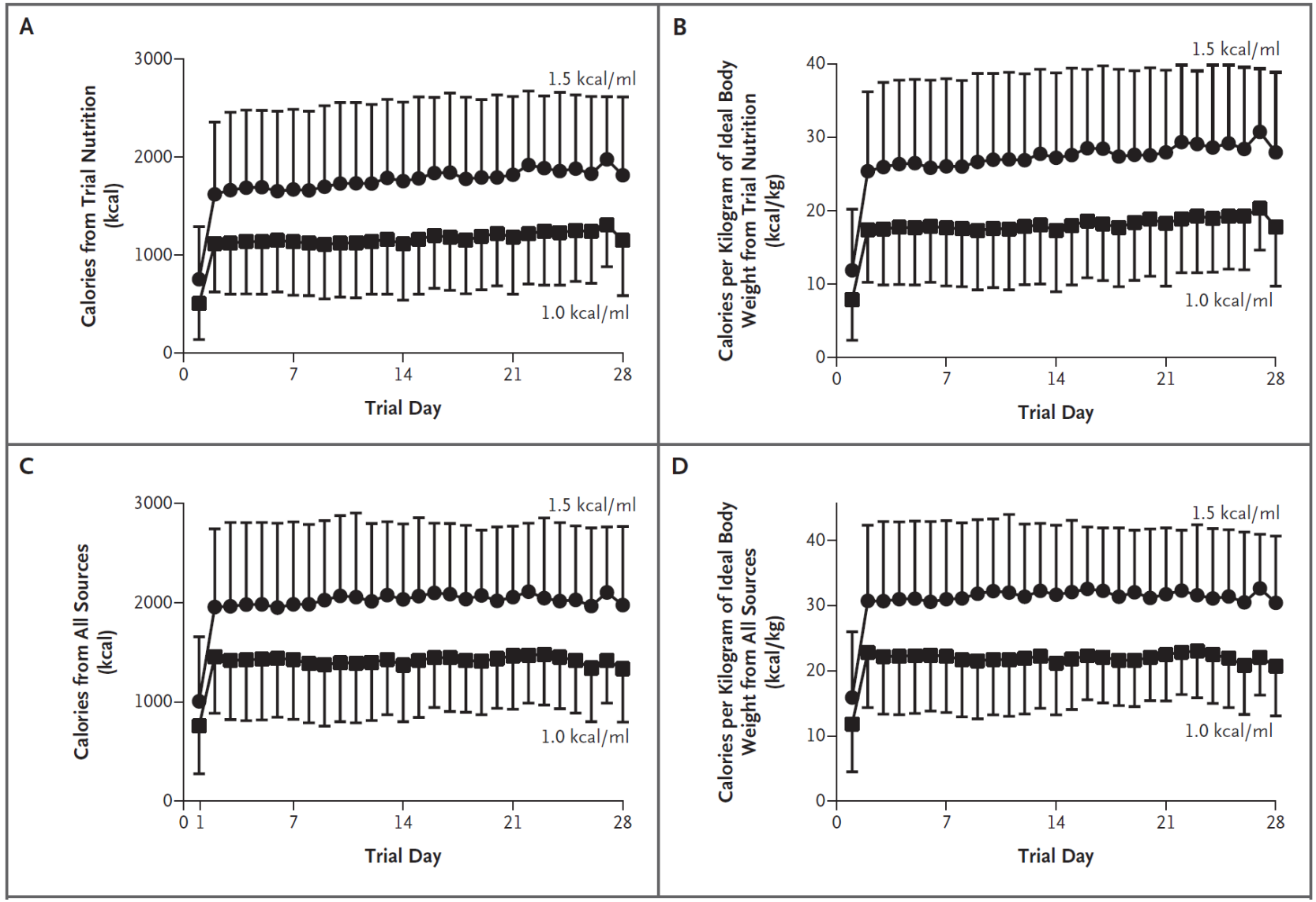
| Outcome | 1.5-kcal Group | 1.0-kcal Group | Difference or Relative Risk (95% CI)* |
|---|---|---|---|
| Primary outcome: death by day 90 — no./total no. (%) | 523/1948 (26.8) | 505/1966 (25.7) | 1.05 (0.94 to 1.16)† |
| Secondary outcomes | | | |
| Death by the time of hospital discharge — no./total no. (%) | 468/1967 (23.8) | 470/1981 (23.7) | 1.00 (0.97 to 1.04) |
| Death by day 28 — no./total no. (%) | 450/1961 (22.9) | 455/1976 (23.0) | 1.00 (0.89 to 1.12) |
| Median days alive and not in ICU (IQR)‡ | 17.0 (0 to 23.0) | 17.4 (0 to 23.1) | 0 |
| Median days alive and not in hospital (IQR)‡ | 2.9 (0 to 15.7) | 2.9 (0 to 15.3) | 0 |
| Use and duration of organ support§ | | | |
| Received invasive mechanical ventilation — no./total no. (%) | 1971/1971 (100) | 1982/1984 (99.9) | |
| Median days alive and free of invasive ventilation (IQR) | 20.0 (0 to 25.0) | 20.0 (0 to 25.0) | 0 |
| Received vasopressor support — no./total no. (%) | 1599/1971 (81.1) | 1615/1984 (81.4) | 1.00 (0.97 to 1.03) |
| Median days alive and free of vasopressor support (IQR) | 23.0 (2.0 to 26.0) | 23.0 (4.0 to 26.0) | 0 |
| Received renal replacement therapy — no./total no. (%) | 367/1946 (18.9) | 361/1955 (18.5) | 1.02 (0.90 to 1.16) |
| Median days alive and free of renal replacement therapy (IQR) | 28.0 (8.0 to 28.0) | 28.0 (10.0 to 28.0) | 0 |
| Microbiology — no./total no. (%)¶ | | | |
| Positive blood cultures | 228/1971 (11.6) | 221/1984 (11.1) | 1.04 (0.87 to 1.24) |
| Administration of intravenous antimicrobial agent | 1662/1971 (84.3) | 1658/1985 (83.5) | 1.01 (0.98 to 1.04) |
| Adverse events — no./total no. of adverse events‖ | | | |
| Electrolyte abnormality | 45/69 | 42/63 | |
| Gastrointestinal event | 22/69 | 20/63 | |
| Other | 2/69 | 1/63 | |
| Serious adverse events — no./total no.‖ | 1/1971 | 1/1986 | |

N Engl J Med 2018;379:1823-34.

**Table 2. Daily Nutrition Delivery up to Day 28.***

| Measure | 1.5-kcal Group (N=1971) | 1.0-kcal Group (N=1985)† | Difference or Relative Risk (95% CI)‡ |
|---|---|---|---|
| Median time from ICU admission to commencing trial nutrition (IQR) — hr | 15.8 (7.7 to 26.3) | 15.9 (7.9 to 28.3) | −0.4 (−1.1 to 0.4) |
| Median duration of trial nutrition (IQR) — days§ | 6.0 (3.0 to 11.0) | 6.0 (3.0 to 11.0) | 0 |
| Volume of trial nutrition delivered — ml/day¶ | 1242±318 | 1262±313 | −20 (−40 to 0) |
| Percentage of trial target rate delivered | 81±17 | 82±16 | −1 (−2 to 0) |
| Calories delivered — kcal/day¶ | | | |
| Trial nutrition | 1863±478 | 1262±313 | 601 (576 to 626) |
| Trial nutrition plus other sources‖ | 1930±547 | 1407±397 | 523 (493 to 553) |
| Calories delivered — kcal/kg of ideal body weight per day¶ | | | |
| Trial nutrition | 29.1±6.2 | 19.6±4.0 | 9.5 (9.2 to 9.9) |
| Trial nutrition plus other sources‖ | 30.2±7.5 | 21.9±5.6 | 8.3 (7.9 to 8.7) |
| Calories delivered — kcal/kg of actual body weight per day¶** | | | |
| Trial nutrition | 23.1±7.1 | 15.6±4.8 | 7.5 (7.1 to 7.9) |
| Trial nutrition plus other sources‖ | 23.9±7.8 | 17.4±5.5 | 6.6 (6.2 to 7.0) |
| Protein delivered¶ | | | |
| Trial nutrition — g/day | 69.6±17.8 | 69.4±17.2 | 0.1 (−1.0 to 1.2) |
| Trial nutrition — g/kg of ideal body weight per day | 1.09±0.22 | 1.08±0.23 | 0.01 (−0.01 to 0.02) |
| Gastrointestinal tolerance | | | |
| Median largest gastric residual volume (IQR) — ml†† | 250 (100 to 441) | 180 (65 to 360) | 40 (30 to 50) |
| Regurgitation or vomiting — no./total no. (%)‡‡ | 370/1959 (18.9) | 309/1966 (15.7) | 1.20 (1.05 to 1.38) |
| Receipt of promotility agents — no./total no. (%)‡‡ | 929/1959 (47.4) | 779/1966 (39.6) | 1.20 (1.11 to 1.29) |
| Median bowel movements per day (IQR)‡‡§§ | 0.5 (0 to 1.3) | 0.6 (0 to 1.3) | 0 |
| Median insulin administration (IQR) — IU/day¶¶ | 3.0 (0 to 41.8) | 0 (0 to 30.6) | 0 |
| Median highest daily blood glucose concentration (IQR) — mg/dl¶¶ | 225.2 (185.6 to 277.4) | 212.6 (174.7 to 261.2) | 12.6 (9.0 to 18.0) |

N Engl J Med 2018;379:1823-34.




N Engl J Med 2018;379:1823-34.

ORIGINAL ARTICLE

Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*

# Závěr

- Zvýšení energetického příjmu, bez zvýšení příjmu proteinů použitím hyperkalorického přípravku (1,5 kcal/ml) nesnižuje mortalitu dospělých kriticky nemocných pacientů.
- Hyperkalorická výživa byla hůř tolerována a byla spojena s vyšší hladinou glykémie
- Hyperkalorická výživa vedla k 50% zvýšení denního příjmu energie

N Engl J Med 2018;379:1823-34.

# Sedace, delirium, QoC

ORIGINAL ARTICLE

# Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

SPICE III

N Engl J Med 2019;380:2506-17.

ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

# Design

- Multicentrická randomizovaná nezaslepená studie
- Ventilovaní pacienti >24 hodin s nasazenou sedací
- 1948/1956 pacientů
- Cíl sedace RASS -2 – 1
- DEX 1- 1,5 mcg/kg/hod vs. standardní sedace

N Engl J Med 2019;380:2506-17.

ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

# Outcome

- Primární : 90- denní mortalita
- Sekundární:
  - 180 denní mortalita
  - Transfer na LDN
  - Kognitivní funkce za 180 dní (Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)
  - European Quality of Life 5-Dimensions 3-Level questionnaire (EQ-5D-3L)
  - Dny bez komatu
  - Dny bez deliria
- Terciální a periprocedurální outcomy:
  - cíle sedace, analgetika, sedativa, AE

N Engl J Med 2019;380:2506-17.

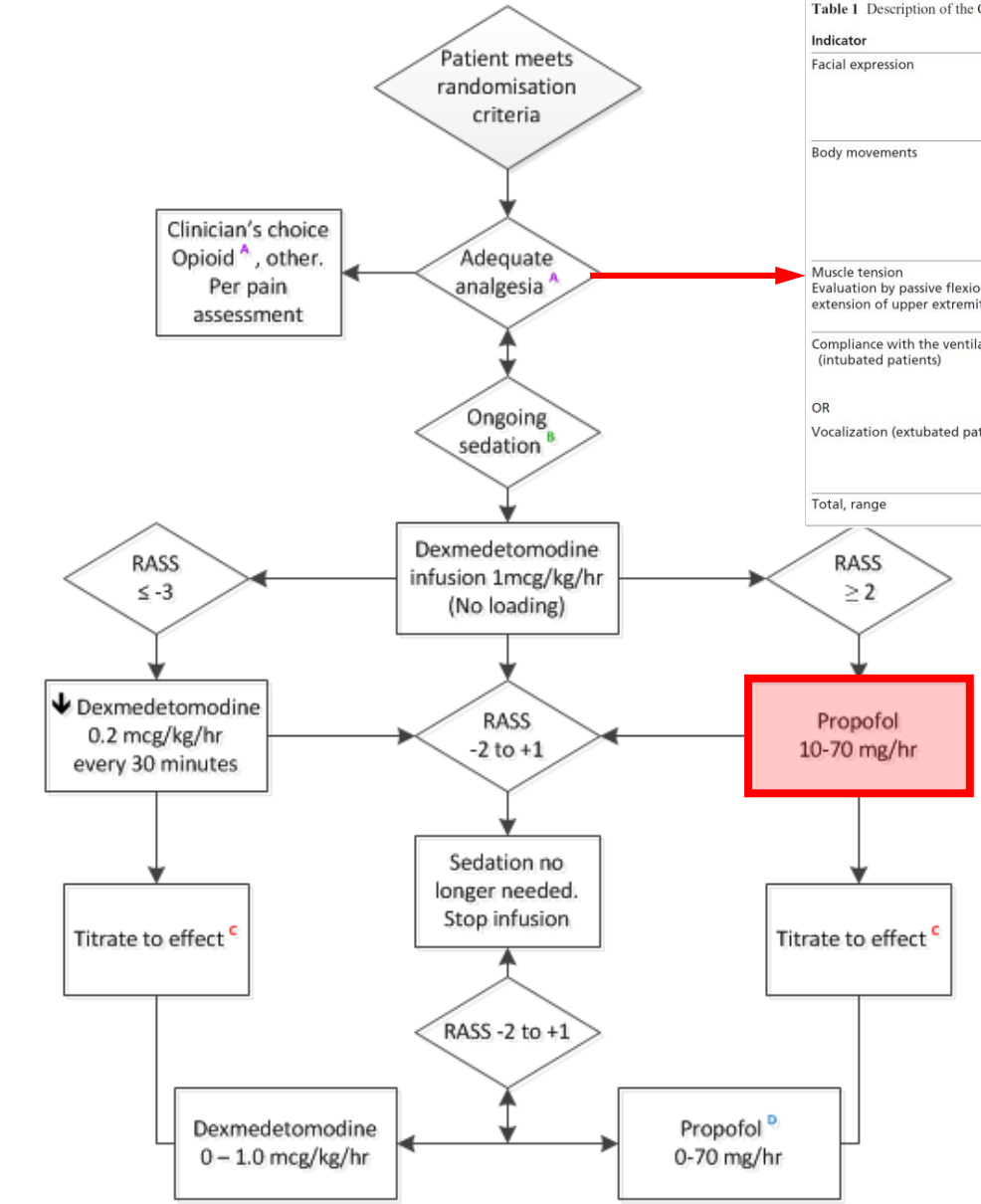
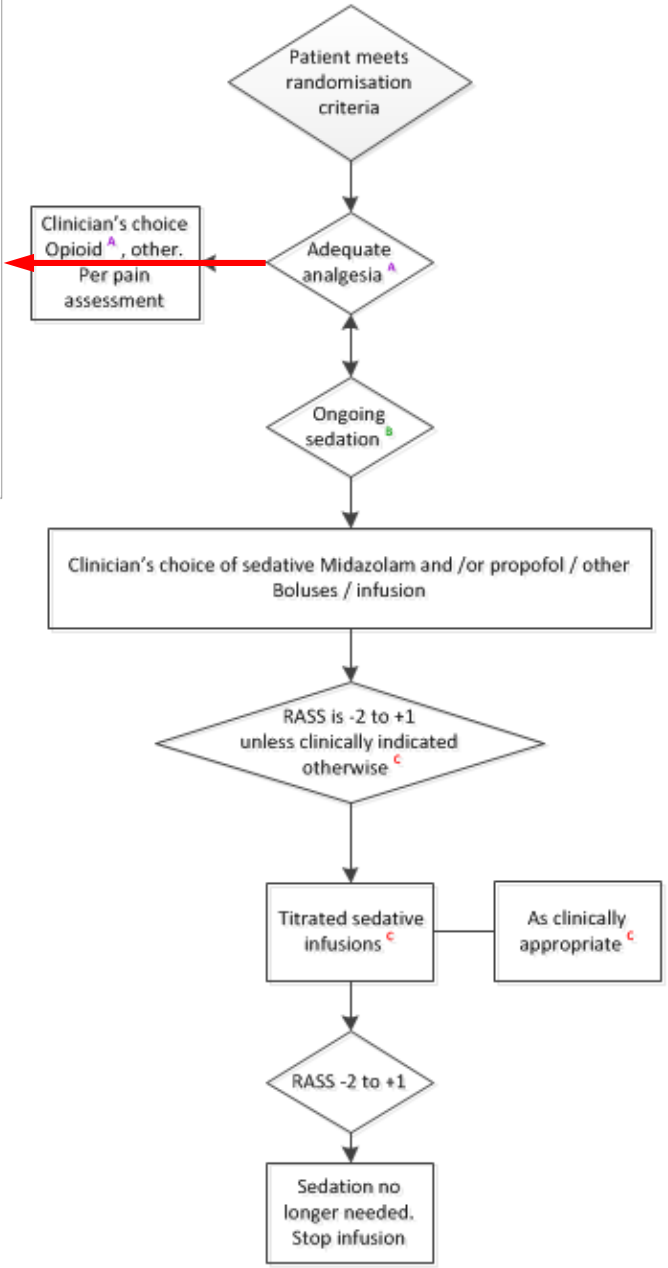



**Table 1** Description of the Critical-Care Pain Observation Tool

| Indicator | Description | Score | |
|---|---|---|---|
| Facial expression | No muscular tension observed | Relaxed, neutral | 0 |
| | Presence of frowning, brow lowering, orbit tightening, and levator contraction | Tense | 1 |
| | All of the above facial movements plus eyelid tightly closed | Grimacing | 2 |
| Body movements | Does not move at all (does not necessarily mean absence of pain) | Absence of movements | 0 |
| | Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements | Protection | 1 |
| | Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed | Restlessness | 2 |
| Muscle tension<br>Evaluation by passive flexion and extension of upper extremities | No resistance to passive movements | Relaxed | 0 |
| | Resistance to passive movements | Tense, rigid | 1 |
| | Strong resistance to passive movements, inability to complete them | Very tense or rigid | 2 |
| Compliance with the ventilator (intubated patients)<br>OR | Alarms not activated, easy ventilation | Tolerating ventilator or movement | 0 |
| | Alarms stop spontaneously | Coughing but tolerating | 1 |
| | Asynchrony: blocking ventilation, alarms frequently activated | Fighting ventilator | 2 |
| Vocalization (extubated patients) | Talking in normal tone or no sound | Talking in normal tone or no sound | 0 |
| | Sighing, moaning | Sighing, moaning | 1 |
| | Crying out, sobbing | Crying out, sobbing | 2 |
| Total, range | | | 0-8 |




A: Opioids can be given by infusion or boluses and continued as needed throughout study period, the use of remifentanil is not permitted.
B: Benzodiazepines in all forms and injectable clonidine are precluded.
C: Reduce propofol first 20mg / hr every 15 minutes to lowest effective dose required.
D: If RASS ≥ 2 (agitation) continues, propofol can be titrated up to 200 mg/hr.

A: Opioids can be given by infusion or boluses and continued as needed throughout study period, the use of remifentanil is not permitted.
B: Dexmedetomidine and injectable clonidine are precluded.
C: RASS -2 to +1 is encouraged. Midazolam and/or Propofol [illegible]

N Engl J Med 2019;380:2506-17.

**Table 2. Clinical Outcomes.***

| Outcome | Dexmedetomidine (N=1948) | Usual Care (N=1956) | Odds Ratio (95% CI) | Adjusted Risk Difference (95% CI)† |
|---|---|---|---|---|
| Death from any cause at 90 days: primary outcome — no. (%) | 566 (29.1) | 569 (29.1) | 1.00 (0.87 to 1.15) | 0.0 (–2.9 to 2.8) |
| Secondary outcomes | | | | |
| Death at 180 days — no./total no. (%) | 609/1935 (31.5) | 610/1946 (31.3) | 1.01 (0.88 to 1.16) | 0.1 (–2.8 to 3.1) |
| Institutional dependency at 180 days — no./total no. (%) | 89/1323 (6.7) | 94/1337 (7.0) | 0.96 (0.73 to 1.27) | –0.3 (–2.1 to 1.5) |
| Mean score on Short IQCODE at 180 days (95% CI)‡ | 3.14 (3.11 to 3.17) | 3.08 (3.05 to 3.11) | | 0.06 (0.02 to 0.11) |
| Mean score on the EQ-5D-3L questionnaire (95% CI)§ | 69.8 (68.5 to 71.1) | 70.2 (69.0 to 71.5) | | –0.4 (–2.2 to 1.3) |
| Median no. of days free from coma or delirium (IQR)¶ | 24.0 (11.0 to 26.0) | 23.0 (10.0 to 26.0) | | 1.0 (0.5 to 1.5) |
| Median no. of ventilator-free days (IQR)¶ | 23.0 (0.0 to 26.0) | 22.0 (0.0 to 25.0) | | 1.0 (0.4 to 1.6) |

N Engl J Med 2019;380:2506-17.

**Table S7 - Tertiary and Process Related Outcomes**

| Outcome | DEX N=1954 | Usual Care N=1964 | Odds Ratio † 95%CI |
|---|---|---|---|
| Mortality at hospital discharge N (%) | 506/1952 (25.9) | 513/1962 (26.1) | 0.99 (0.86-1.14) |
| Median hospital LOS d (IQR) | 13.5 (7.0-25.9) | 13.2 (7.3-26.1) | 0.99 (0.92-1.07)* |
| Mortality at ICU discharge N (%) | 410/1952 (21.0) | 410/1963 (20.9) | 1.01 (0.86-1.18) |
| Median ICU LOS d (IQR) | 6.0 (3.1-11.2) | 6.3 (3.2-12.3) | 1.00 (0.93-1.07)* |
| Median duration of ventilation days, (IQR): all | 3.0 (1.5-7.1) N=1942 | 3.3 (1.7-8.0) N=1958 | |
| survivors | 2.8 (1.4-6.2) N=1439 | 3.0 (1.7-6.9) N=1445 | |
| non-survivors | 4.4 (1.7-9.5) N=503 | 5.1 (1.8-11.3) N=514 | |
| Median days coma-free (IQR) ‖ | 25 (14-27) | 24 (14-26) | |
| Delirium at any point during stay N (%)‖ | 796 (40.7) | 835 (42.5) | 0.93 (0.82-1.06) |
| Tracheostomy N (%)‖ | 231 (11.8) | 266/1963 (13.6) | 0.85 (0.71-1.03) |
| Physical restraints N (%)‖ | 490 (25.1) | 501/1963 (25.5) | 0.98 (0.85-1.13) |
| Unplanned extubation N (%)‖ | 87 (4.5) | 70 (3.6) | 1.26 (0.91-1.74) |
| Re-intubation N (%)‖ | 285 (14.6) | 232/1962 (11.8) | 1.27 (1.06-1.53) |
| Active mobilization N (%)‖ | 1110 (56.8) | 1125/1963 (57.3) | 0.98 (0.86-1.11) |
| Readmission to ICU N (%) | 169/1542 (11.0) | 140/1553 (9.0) | 1.24 (0.98-1.57) |

N Engl J Med 2019;380:2506-17.

**Table S8: Post Randomization Sedative, Analgesic and Adjunct Medications**

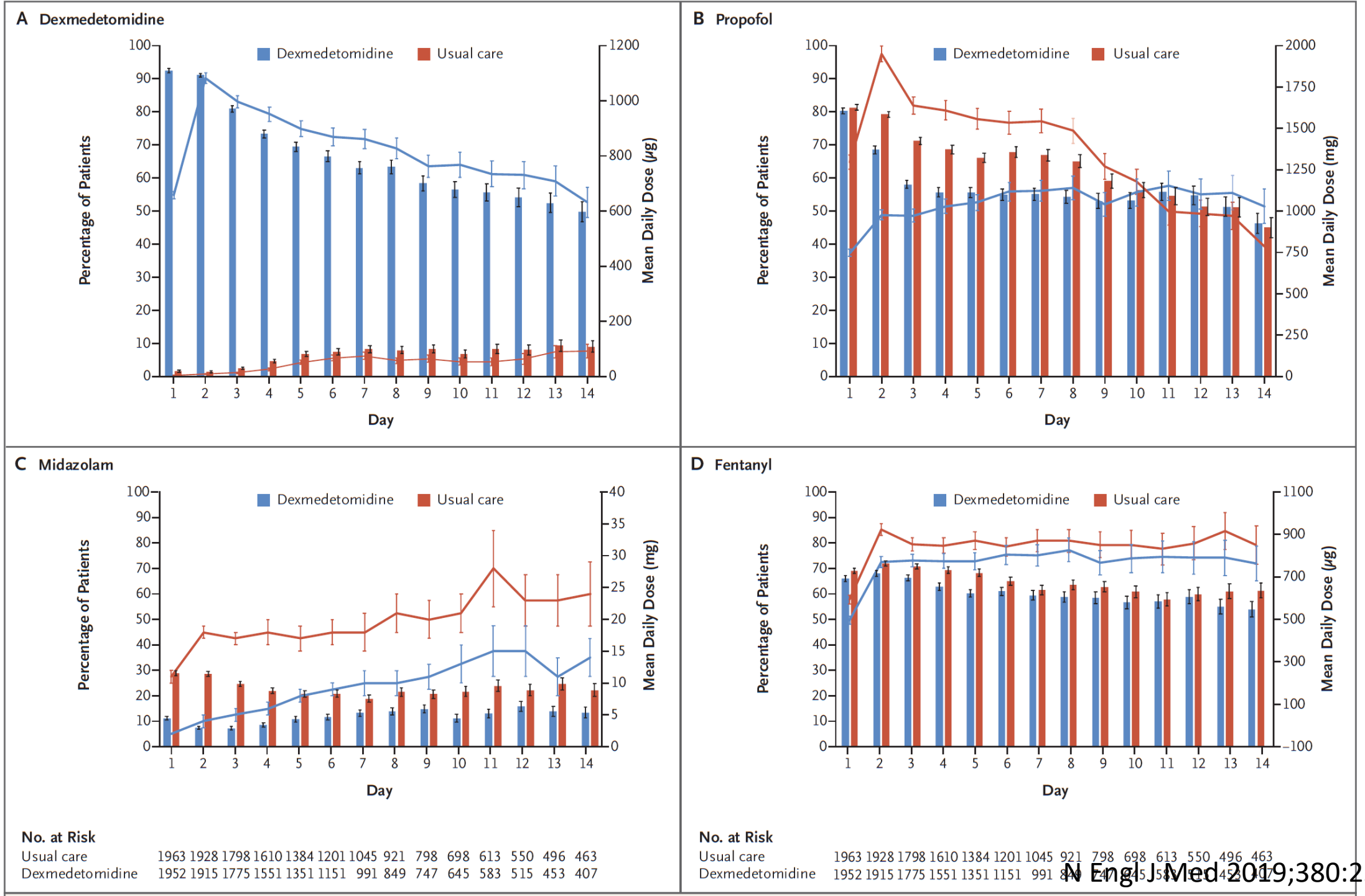
| Medication ¶ ¶ | DEX ¶ N=1954 | Usual Care ¶ N=1964 |
|---|---|---|
| Dexmedetomidine | | |
| Patients N (%) | 1910 (97.8) | 226 (11.5) |
| Median duration of infusion [IQR] d | 2.56 [1.10 to 5.32] | 1.26 [0.67 to 3.29] |
| Propofol | 9.51 mg/kg (IQR 4.20 - 18.70) | 17.9 mg/kg (IQR 8.90 - 30.50) |
| Patients N (%) | 1679 (86.0) | 1741 (88.7) |
| Median duration of infusion [IQR] d | 1.95 [0.79 to 4.66] | 2.67 [1.36 to 5.70] |
| Midazolam | 0.11 mg/kg (IQR, 0.04 - 0.43) | 0.31 m/kg (IQR 0.10 - 0.70) |
| Patients N (%) | 455 (23.3) | 794 (40.4) |
| Median duration of infusion [IQR] d | 0.50 [0.21 to 1.87] | 1.51 [0.67 to 3.17] |
| Fentanyl | | |
| Patients N (%) | 1534 (78.5) | 1584 (80.7) |
| Morphine | | |
| Patients N (%) | 580 (29.7) | 613 (31.2) |
| Alfentanil | | |
| Patients N (%) | 152 (7.8) | 146 (7.4) |
| Haloperidol | | |
| Patients N (%) | 236 (12.1) | 277 (14.1) |
| Neuromuscular blockade (NMB) N (%) * | 684 (35.0) | 692 (35.3) |
| NMB for ≥ 2 consecutive days N (%) | 265 (13.6) | 278 (14.2) |
| Indication for benzodiazepines in DEX arm ** | | |
| Uncontrolled agitation/delirium N (%) | 41 (2.1) | - |
| Concomitant NMB N (%) | 102 (5.2) | - |
| Seizures N (%) | 26 (1.3) | - |
| Palliation N (%) | 109 (5.6) | - |
| Procedural sedation N (%) | 138 (7.1) | - |

N Engl J Med 2019;380:2506-17.

**Table S9 –Reported Adverse and Serious Adverse Events[¥]**

| | DEX (N=1954) | Usual care (N=1964) | P value |
|---|---|---|---|
| One or more AE during study | 188 (9.6%) | 35 (1.8%) | < 0.0001 |
| One or more SAE during study | 52 (2.7%) | 7 (0.4%) | < 0.0001 |
| **Adverse Events:** | | | |
| Bradycardia | 99 (5.1%) | 9 (0.5%) | < 0.0001 |
| Hypotension | 52 (2.7%) | 10 (0.5%) | < 0.0001 |
| Other AE | 44 (2.3%) | 16 (0.8%) | < 0.0001 |
| **Serious Adverse Events:** | | | |
| Bradycardia | 13 (0.70%) | 1 (0.05%) | 0.001 |
| Hypotension | 10 (0.50%) | 1 (0.05%) | 0.006 |
| Prolonged sinus pause (Asystole) | 14 (0.70%) | 2 (0.10%) | 0.003 |
| Other SAE | 16 (0.82%) | 3 (0.15%) | 0.003 |
| Uncontrolled agitation during study | 44 (2.3%) | 77 (3.9%) | 0.003 |
| Protocol deviation during study | 360(18.4%) | 214 (10.9%) | < 0.0001 |

N Engl J Med 2019;380:2506-17.




N Engl J Med 2019;380:2506-17.

ORIGINAL ARTICLE

# Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, E.E. Bass, S. Bin Kadiman, C.J. McArt, M.P. Wise, and S.A. and

In conclusion, among critically ill adults undergoing mechanical ventilation in the ICU, the early administration of dexmedetomidine as the sole or primary sedative did not result in lower 90-day mortality than usual care. Dexmedetomidine was insufficient alone or as the primary agent to achieve clinically desired target sedation levels and was associated with more reported adverse events than usual care.

N Engl J Med 2019;380:2506-17.

# Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM[1]; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN[2,3]; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC[4]; Jennifer L. Thompson, MPH[5]; J. Matthew Aldrich, MD[6]; Juliana Barr, MD, FCCM[7,8]; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM[9]; Shannon S. Carson, MD[10]; John W. Devlin, PharmD, FCCM[11]; Heidi J. Engel, PT, DPT[12]; Cheryl L. Esbrook, OTR/L, BCPR[13]; Ken D. Hargett, MHA, FAARC, FCCM[14]; Lori Harmon, RRT, MBA, CPHQ[15]; Christina Hielsberg, MA[15]; James C. Jackson, PsyD[1]; Tamra L. Kelly, BS, RRT, MHA[4]; Vishakha Kumar, MD, MBA[15]; Lawson Millner, RRT[16]; Alexandra Morse, PharmD[4]; Christiane S. Perme, PT, CCS, FCCM[14]; Patricia J. Posa, BSN, MSA, CCRN-K[17]; Kathleen A. Puntillo, PhD, RN, FCCM, FAAN[18]; William D. Schweickert, MD[19]; Joanna L. Stollings, PharmD, FCCM[20]; Alai Tan, PhD[2]; Lucy D'Agostino McGowan, PhD[21]; E. Wesley Ely, MD, MPH, FCCM[1,22]

Crit Care Med 2019; 47:3–14)

**Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults**

Brenda T. Pun, DNP, RN, FCCM[1]; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN[2,3];

# Design

- Prospektivní, multicentrická kohortová studie
- 68 univerzitních, komunitních a státních ICU, 20 měsíců
- 15,226 pacientů
- Vyhodnocení kompletního splnění ABCDEF bundles
- Percentuální vyhodnocení splnění jednotlivých složek

Crit Care Med 2019; 47:3–14)

# ABCDEF bundles

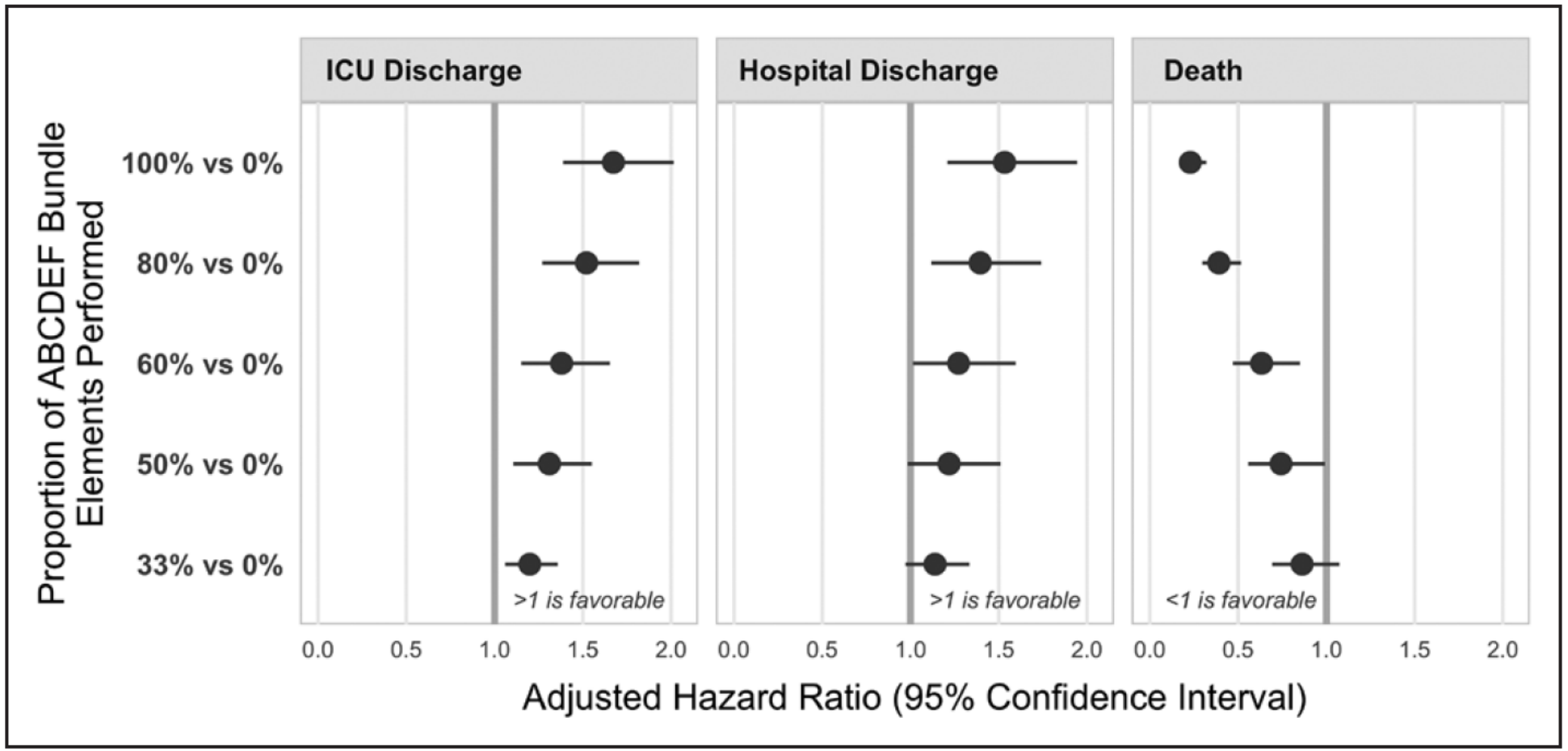
- ***A***ssess, prevent, and manage pain;
- ***B***oth spontaneous awakening and breathing trials
- ***C***hoice of Analgesia and Sedation
- ***D***elirium assess, prevent,vand manage
- ***E***arly Mobility and Exercise
- ***F***amily engagement/empowerment

Crit Care Med 2019; 47:3–14)

**TABLE 2. Outcomes for Patients With Complete (vs Incomplete) ABCDEF Bundle Performance: Data are Adjusted Hazard Ratios and Adjusted Odds Ratios**

| Outcomes | Complete Bundle Performance | *p* Value |
|---|---|---|
| **Patient-Related Outcomes** | **Adjusted Hazard Ratio (95% CI)** | |
| ICU discharge[a] | 1.17 (1.05–1.30) | < 0.004 |
| Hospital discharge[b] | 1.19 (1.01–1.40) | < 0.033 |
| Death[c] | 0.32 (0.17–0.62) | < 0.001 |
| **Symptom-Related Outcomes[d]** | **AOR (95%CI)** | |
| Mechanical ventilation | 0.28 (0.22–0.36) | < 0.0001 |
| Coma | 0.35 (0.22–0.56) | < 0.0001 |
| Delirium | 0.60 (0.49–0.72) | < 0.0001 |
| Significant pain | 1.03 (0.88–1.21) | 0.7000 |
| Physical restraints | 0.37 (0.30–0.46) | < 0.0001 |
| **System-Related Outcomes** | **AOR (95%CI)** | |
| ICU readmission[e] | 0.54 (037–0.79) | < 0.001 |
| Discharge destination[f] | 0.64 (0.51–0.80) | < 0.001 |

Crit Care Med 2019; 47:3–14)

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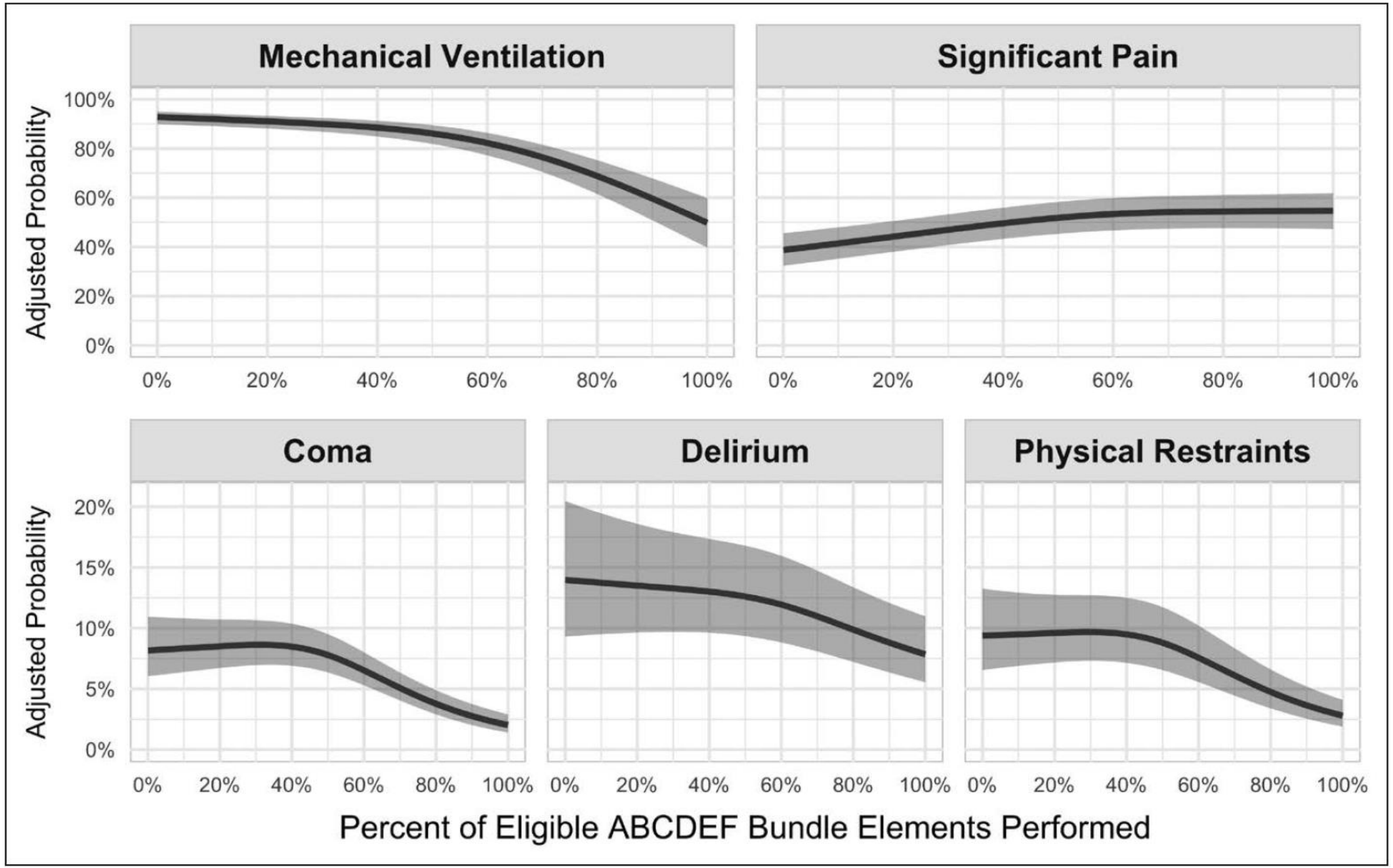


Crit Care Med 2019; 47:3–14)

This cohort analysis from the ICU Liberation Collaborative demonstrates that the performance of the ABCDEF bundle results in significant and dose-related improvements in outcomes, including better survival, duration of mechanical ventilation, brain organ dysfunction (i.e., delirium and coma), physical restraint use, ICU readmission rates, and discharge disposition of ICU survivors. Additional unmeasured benefits often expressed during the collaborative represent excellent points for future work, such as the effect that full integration of the ABCDEF bundle has on making ICU care more collaborative, holistic, and patient centered, with an eye toward returning patients to their previous lives.

Crit Care Med 2019; 47:3–14)