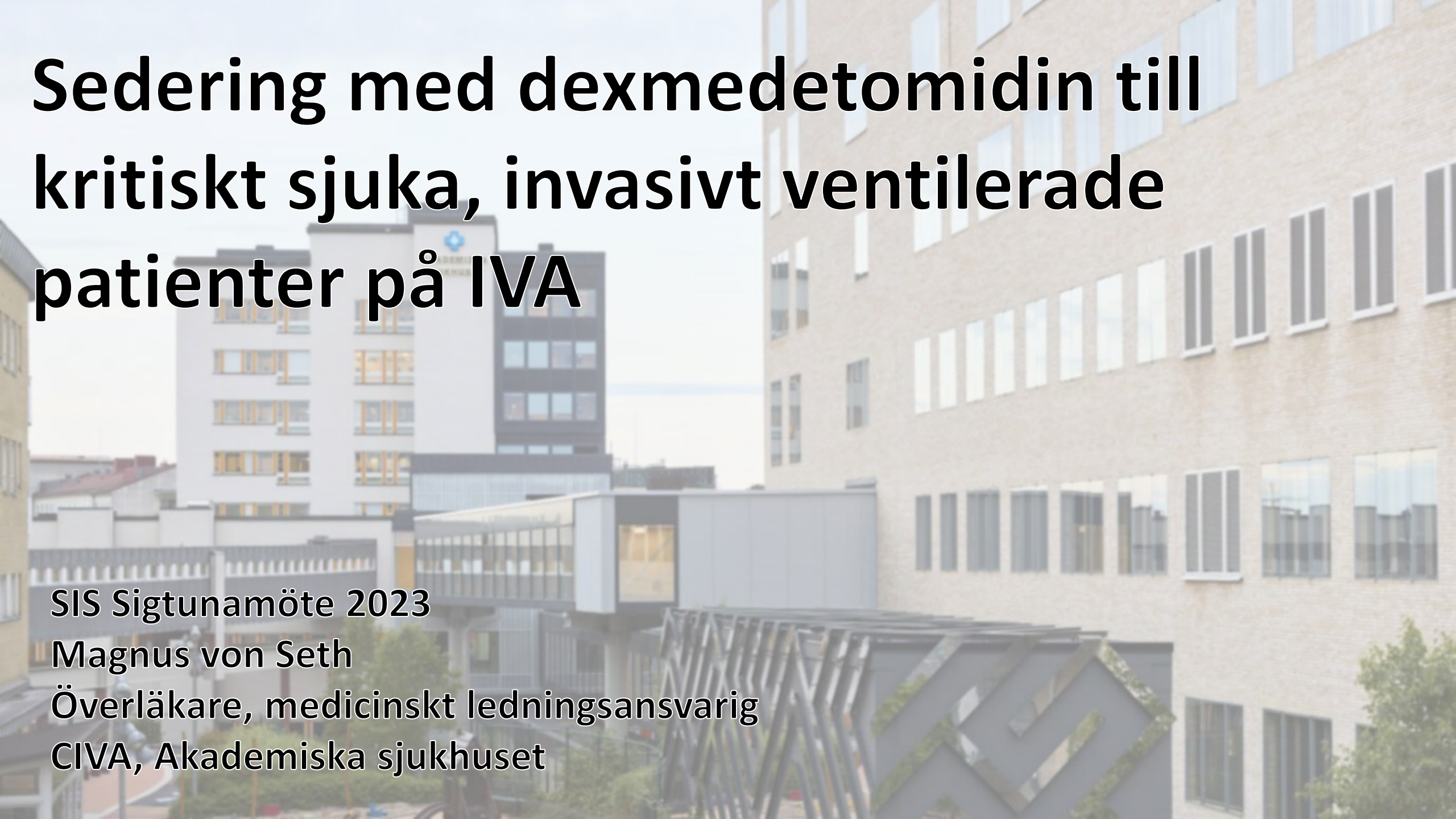
Sedering med dexmedetomidin till kritiskt sjuka, invasivt ventilerade patienter på IVA



SIS Sigtunamöte 2023
Magnus von Seth
Överläkare, medicinskt ledningsansvarig
CIVA, Akademiska sjukhuset

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38]; Richard R. Riker, MD, FCCM[29]; Bryce R. H. Robinson, MD, MS, FACS, FCCM[39]; Yahya Shehabi, MD, PhD, FCICM[40]; Paul M. Szumita, PharmD, FCCM[41]; Chris Winkelman, RN, PhD, FCCM[42]; John E. Centofanti, MD, MSc[43]; Carrie Price, MLS[44]; Sina Nikayin, MD[45]; Cheryl J. Misak, PhD[46]; Pamela D. Flood, MD[47]; Ken Kiedrowski, MA[48]; Waleed Alhazzani, MD, MSc (Methodology Chair)[16,49]

Critical Care Medicine 46(9):p e825-e873, September 2018.

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Medical and Surgical Patients Not Undergoing Cardiac Surgery

Rationale: We evaluated the effect of propofol versus benzodiazepine, dexmedetomidine versus benzodiazepine, and propofol versus dexmedetomidine in three separate analyses for the outcomes deemed critical. In most studies, benzodiazepines were administered as continuous infusions and not intermittent boluses. We combined studies using midazolam and lorazepam. In critically ill, mechanically ventilated patients, a shortened time to light sedation of at least 4 hours and time to extubation of at least 8–12 hours (one nursing shift) were deemed clinically significant.

!

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38]; Richard R. Riker, MD, FCCM[29]; Bryce R. H. Robinson, MD, MS, FACS, FCCM[39]; Yahya Shehabi, MD, PhD, FCICM[40]; Paul M. Szumita, PharmD, FCCM[41]; Chris Winkelman, RN, PhD, FCCM[42]; John E. Centofanti, MD, MSc[43]; Carrie Price, MLS[44]; Sina Nikayin, MD[45]; Cheryl J. Misak, PhD[46]; Pamela D. Flood, MD[47]; Ken Kiedrowski, MA[48]; Waleed Alhazzani, MD, MSc (Methodology Chair)[16,49]

Critical Care Medicine 46(9):p e825-e873, September 2018.

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Medical and Surgical Patients Not Undergoing Cardiac Surgery

Should dexmedetomidine, when compared with a benzodiazepine, be used for sedation in critically ill, mechanically ventilated adults?

Recommendation: We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence).

?

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38]; Richard R. Riker, MD, FCCM[29]; Bryce R. H. Robinson, MD, MS, FACS, FCCM[39]; Yahya Shehabi, MD, PhD, FCICM[40]; Paul M. Szumita, PharmD, FCCM[41]; Chris Winkelman, RN, PhD, FCCM[42]; John E. Centofanti, MD, MSc[43]; Carrie Price, MLS[44]; Sina Nikayin, MD[45]; Cheryl J. Misak, PhD[46]; Pamela D. Flood, MD[47]; Ken Kiedrowski, MA[48]; Waleed Alhazzani, MD, MSc (Methodology Chair)[16,49]

Critical Care Medicine 46(9):p e825-e873, September 2018.

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Medical and Surgical Patients Not Undergoing Cardiac Surgery

Should dexmedetomidine, when compared with propofol, be used for sedation in critically ill, mechanically ventilated adults?

Recommendation: We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence).

?

Critical Care Medicine 46(9):p e825-e873, September 2018.

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38]; Richard R. Riker, MD, FCCM[29]; Bryce R. H. Robinson, MD, MS, FACS, FCCM[39]; Yahya Shehabi, MD, PhD, FCICM[40]; Paul M. Szumita, PharmD, FCCM[41]; Chris Winkelman, RN, PhD, FCCM[42]; John E. Centofanti, MD, MSc[43]; Carrie Price, MLS[44]; Sina Nikayin, MD[45]; Cheryl J. Misak, PhD[46]; Pamela D. Flood, MD[47]; Ken Kiedrowski, MA[48]; Waleed Alhazzani, MD, MSc (Methodology Chair)[16,49]

!

Recognizing that dexmedetomidine should not be used when deep sedation (with or without neuromuscular blockade) is required, panel members judged that the desirable and undesirable consequences of using propofol (vs dexmedetomidine) were balanced; therefore, they issued a conditional recommendation to use either agents for sedation of critically ill adults. Implementation will likely depend on the availability of the drug and its associated cost at individual institutions.

The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

BACKGROUND

Dexmedetomidine produces sedation while maintaining a degree of arousability and may reduce the duration of mechanical ventilation and delirium among patients in the intensive care unit (ICU). The use of dexmedetomidine as the sole or primary sedative agent in patients undergoing mechanical ventilation has not been extensively studied.

METHODS

In an open-label, randomized trial, we enrolled critically ill adults who had been undergoing ventilation for less than 12 hours in the ICU and were expected to continue to receive ventilatory support for longer than the next calendar day to receive dexmedetomidine as the sole or primary sedative or to receive usual care (propofol, midazolam, or other sedatives). The target range of sedation-scores on the Richmond Agitation and Sedation Scale (which is scored from −5 [unresponsive] to +4 [combative]) was −2 to +1 (lightly sedated to restless). The primary outcome was the rate of death from any cause at 90 days.

RESULTS

We enrolled 4000 patients at a median interval of 4.6 hours between eligibility and randomization. In a modified intention-to-treat analysis involving 3904 patients, the primary outcome event occurred in 566 of 1948 (29.1%) in the dexmedetomidine group and in 569 of 1956 (29.1%) in the usual-care group (adjusted risk difference, 0.0 percentage points; 95% confidence interval, −2.9 to 2.8). An ancillary finding was that to achieve the prescribed level of sedation, patients in the dexmedetomidine group received supplemental propofol (64% of patients), midazolam (3%), or both (7%) during the first 2 days after randomization; in the usual-care group, these drugs were administered as primary sedatives in 60%, 12%, and 20% of the patients, respectively. Bradycardia and hypotension were more common in the dexmedetomidine group.

CONCLUSIONS

Among patients undergoing mechanical ventilation in the ICU, those who received early dexmedetomidine for sedation had a rate of death at 90 days similar to that in the usual-care group and required supplemental sedatives to achieve the prescribed level of sedation. More adverse events were reported in the dexmedetomidine group than in the usual-care group. (Funded by the National Health and Medical Research Council of Australia and others; SPICE III ClinicalTrials.gov number, NCT01728558.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Shehabi at Monash University, School of Clinical Sciences, Level 5, E Block, Monash Medical Centre, Clayton 3168, VIC, Australia, or at yahya.shehabi@monashhealth.org or y.shehabi@unsw.edu.au.

*A complete list of the trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 19, 2019, at NEJM.org.

N Engl J Med 2019;380:2506-17.
DOI: 10.1056/NEJMoa1904710

Intensive Care Med (2021) 47:455–466
https://doi.org/10.1007/s00134-021-06356-8

ORIGINAL

Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial

Yahya Shehabi[1,2*], Ary Serpa Neto[3,4,5,6], Belinda D. Howe[3], Rinaldo Bellomo[3,5,6], Yaseen M. Arabi[7], Michael Bailey[3,5], Frances E. Bass[8,9], Suhaini Bin Kadiman[10], Colin J. McArthur[11], Michael C. Reade[12,13], Ian M. Seppelt[14,15], Jukka Takala[16], Matt P. Wise[17] and Steve A. Webb[3,18] on behalf of The SPICE III Study Investigators

Abstract

Purpose: To quantify potential heterogeneity of treatment effect (HTE), of early sedation with dexmedetomidine (DEX) compared with usual care, and identify patients who have a high probability of lower or higher 90-day mortality according to age, and other identified clusters.

Methods: Bayesian analysis of 3904 critically ill adult patients expected to receive invasive ventilation > 24 h and enrolled in a multinational randomized controlled trial comparing early DEX with usual care sedation.

Results: HTE was assessed according to age and clusters (based on 12 baseline characteristics) using a Bayesian hierarchical models. DEX was associated with lower 90-day mortality compared to usual care in patients > 65 years (odds ratio [OR], 0.83 [95% credible interval [CrI] 0.68–1.00], with 97.7% probability of reduced mortality across broad categories of illness severity. Conversely, the probability of increased mortality in patients ≤ 65 years was 98.5% (OR 1.26 [95% CrI 1.02–1.56]. Two clusters were identified: cluster 1 (976 patients) mostly operative, and cluster 2 (2346 patients), predominantly non-operative. There was a greater probability of benefit with DEX in cluster 1 (OR 0.86 [95% CrI 0.65–1.14]) across broad categories of age, with 86.4% probability that DEX is more beneficial in cluster 1 than cluster 2.

Conclusion: In critically ill mechanically ventilated patients, early sedation with dexmedetomidine exhibited a high probability of reduced 90-day mortality in older patients regardless of operative or non-operative cluster status. Conversely, a high probability of increased 90-day mortality was observed in younger patients of non-operative status. Further studies are needed to confirm these findings.

Keywords: Dexmedetomidine, Sedation, Mechanical ventilation, Mortality, Critically ill

*Correspondence: Yahya.shehabi@monashhealth.org; y.shehabi@unsw.edu.au
[1] Monash Health School of Clinical Sciences, Monash University, Clayton, VIC 3186, Australia
Full author information is available at the end of the article

The names of all participating centers and associated investigators are listed in the Acknowledgements section.

Springer

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

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*

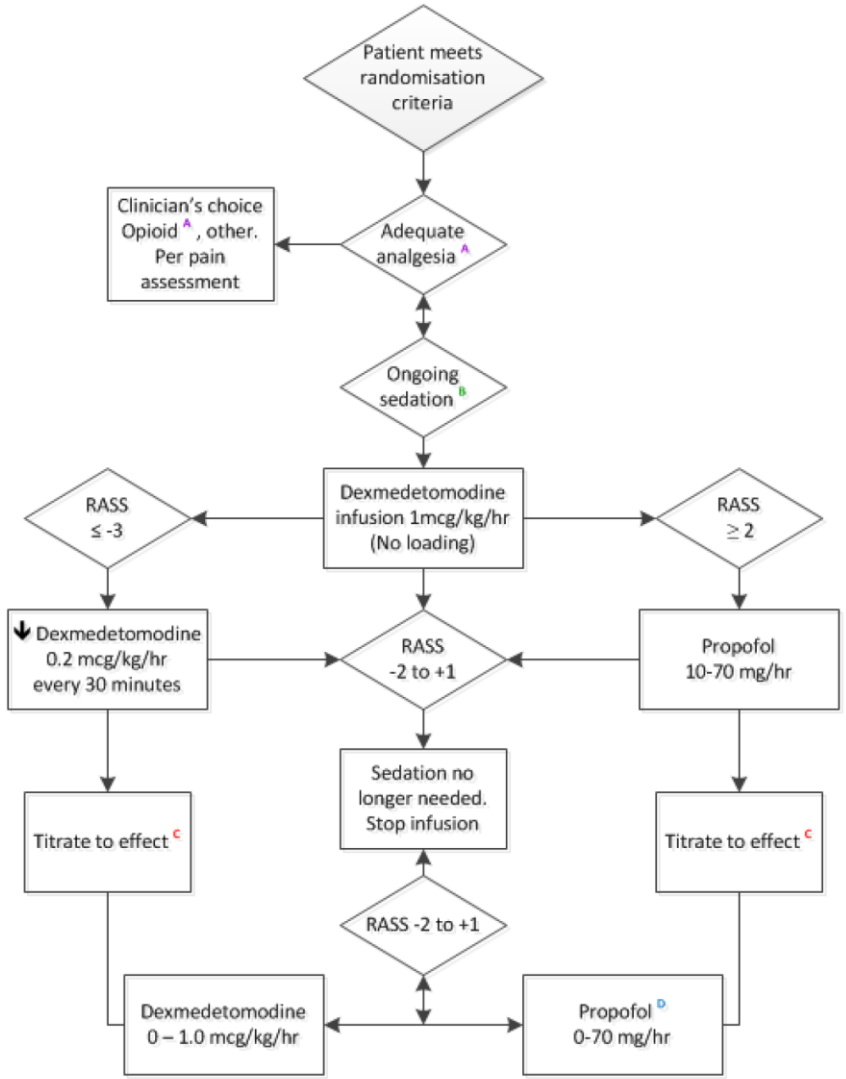
Randomiserad, icke-placebokontrollerad multicenterstudie, 4000 patienter
Interventionsgruppen fick tidigt dexmedetomidin, 1 microg/kg/min, utan bolus med mål att nå ytlig sedering (RASS >-2
Kontrollgruppen fick standardbehandling enligt lokal rutin (midazolam/propofol). Sederingsmål enligt bedömning.
Analgesi gavs till bägge grupperna
Propofol tilläts i interventionsgruppen om sedering motsvarande RASS <-2 behövdes
Primary endpoint var 90-dagars mortalitet, oavsett orsak.

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

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*

Early Dexmedetomidine Sedation Treatment Algorithm (DEX):

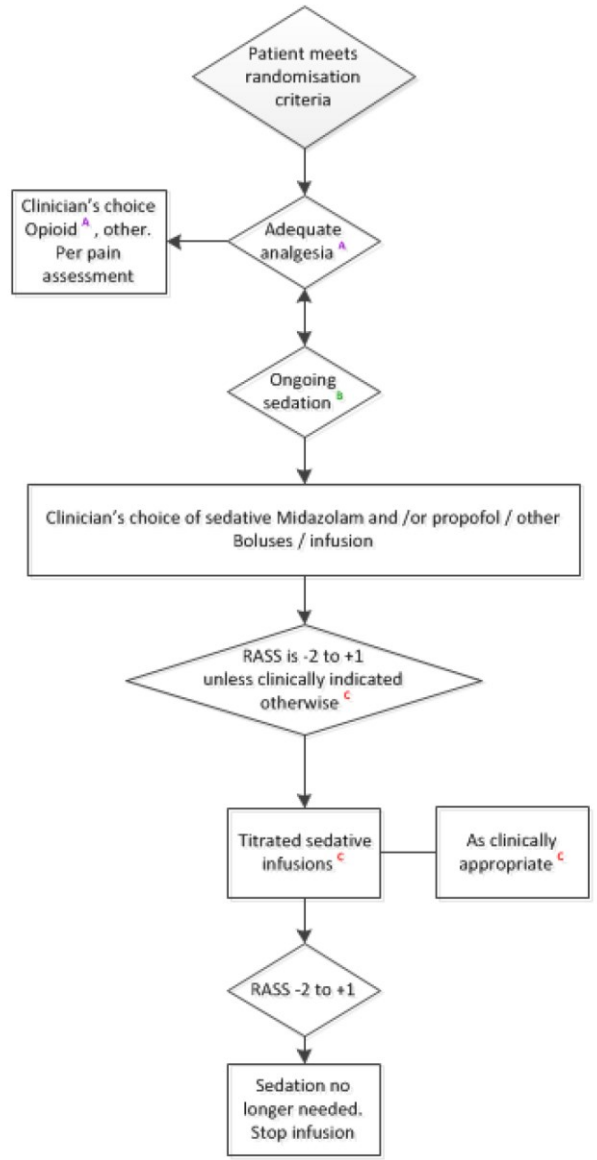


N Engl J Med 2019;380:2506-17.

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*

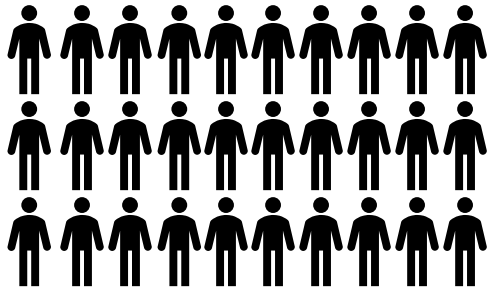
Usual Care Treatment Algorithm:

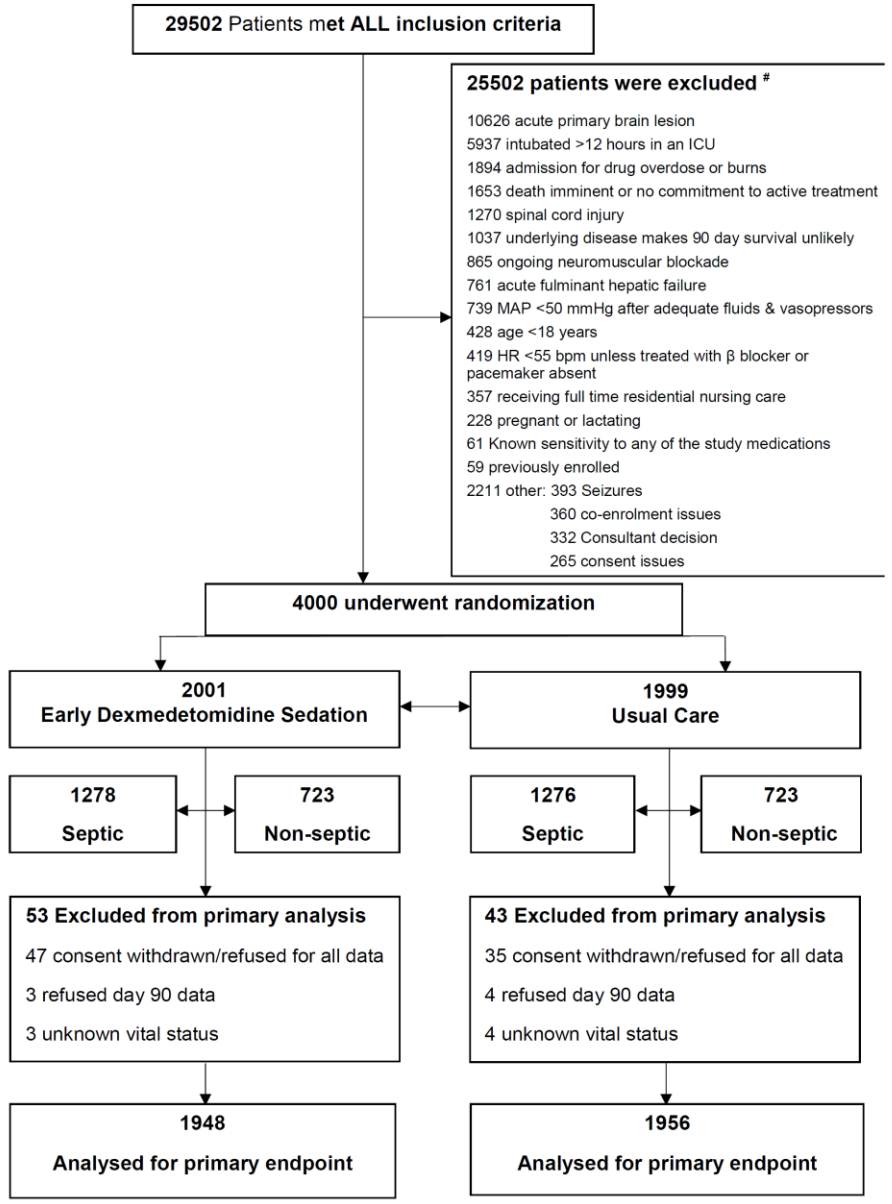


N Engl J Med 2019;380:2506-17.

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*





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

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*

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

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*

Table 2. Clinical Outcomes.*

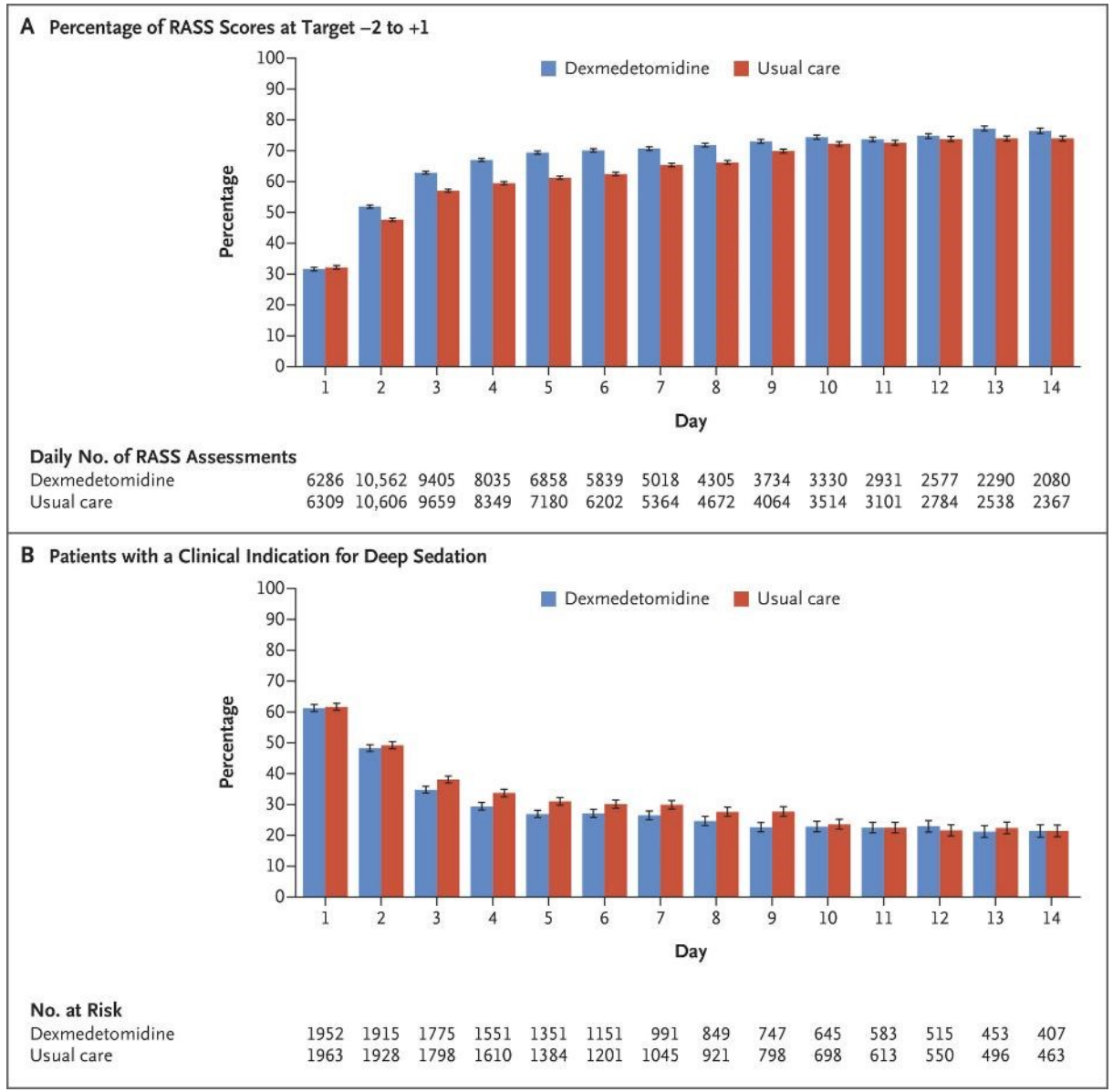
Outcome	Dexmedetomidine (N=1948)	Usual Care (N=1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (–2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	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)

* Data regarding the listed primary and secondary outcomes were censored at 28 days after randomization unless otherwise stated. All tertiary outcomes are described in the Supplementary Appendix.
† Confidence intervals were adjusted for sepsis status but were not adjusted for multiple comparisons.
‡ The Short IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) is a measure of cognitive function as reported by a close friend or relative. The average score on 16 questions is calculated on a scale of 1 to 5, with a score of 3.01 to 3.50 indicating a slight decline and a higher score indicating a worse outcome. This score was evaluated in 1054 patients in the dexmedetomidine group and in 1082 in the usual-care group.
§ Scores on the European Quality of Life 5-Dimensions 3-Level (EQ-5D-3L) questionnaire range from 0 to 100, with higher scores indicating a better quality of life. This score was evaluated in 1144 patients in the dexmedetomidine group and in 1177 in the usual-care group.
¶ The number of days was calculated from the time of randomization to day 28 and was compared by means of quantile regression after adjustment for the sepsis stratum. All the deaths that occurred before day 28 were scored as 0 for ventilator-free days but were scored for the number of days free from coma or delirium on the basis of the 17,282 assessments made with the Confusion Assessment Method for the Intensive Care Unit.

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

Early Sedation with Dexmedetomidine in Critically Ill Patients

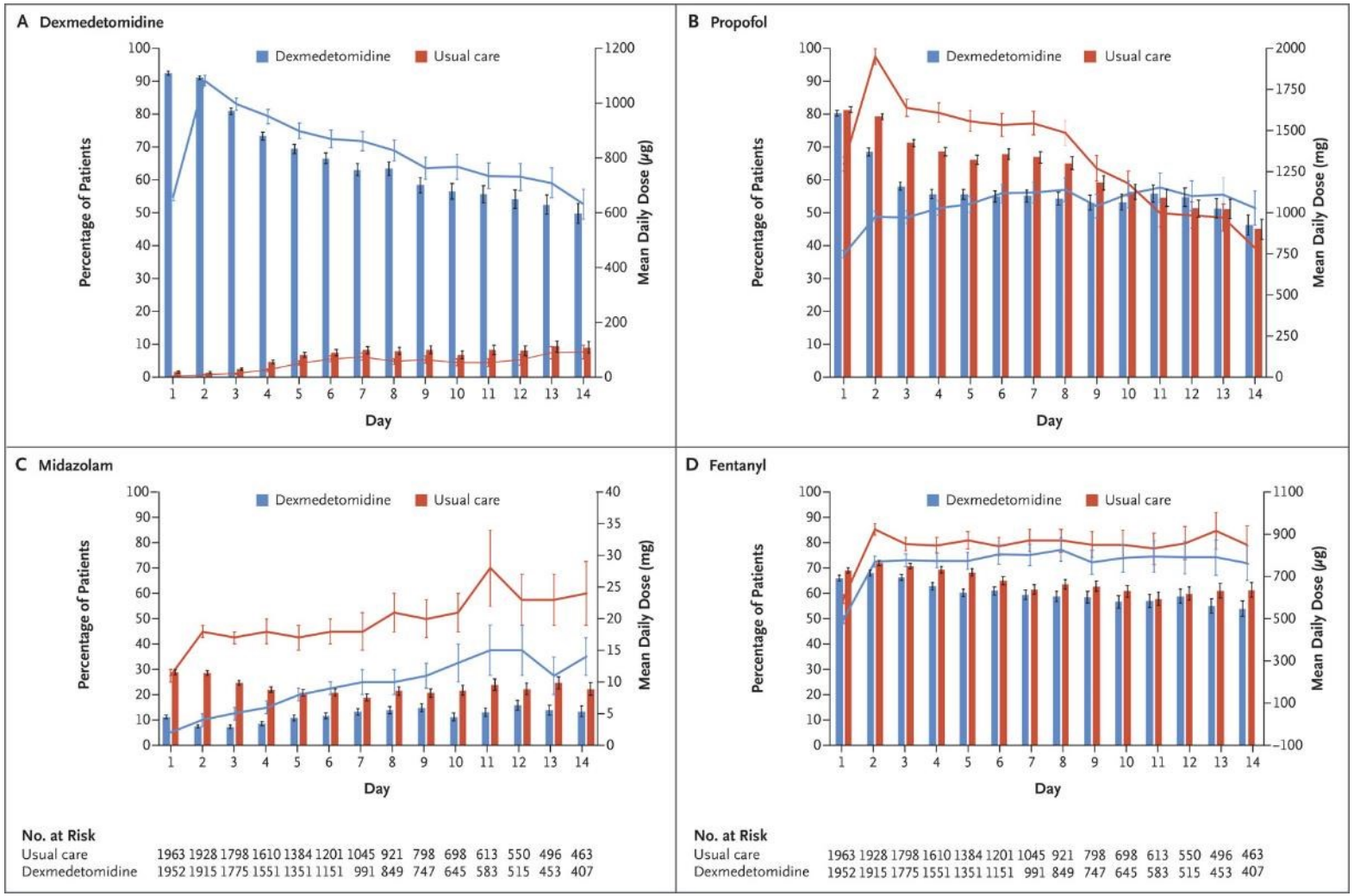
Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*



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

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*



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

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*

fol, 230 (11.9%) received midazolam, and 386 (20.0%) received both as primary sedatives.

During the trial, among the patients in the dexmedetomidine group who received supplemental propofol or midazolam, the median daily dose was 9.51 mg per kilogram (interquartile range, 4.20 to 18.70) and 0.11 mg per kilogram (interquartile range, 0.04 to 0.43), respectively; in the usual-care group, the median daily dose was 17.9 mg per kilogram (interquartile range,

of the critical illness, most patients who were treated with dexmedetomidine received supplemental sedatives. Although the target level of light sedation was observed more frequently in the dexmedetomidine group, deep sedation was frequently reported in the two groups. The number of days that patients were free from coma or delirium and the number of ventilator-free days were 1 day more in the dexmedetomidine group than in the usual-care group for each of the

ifferences did not include zero
ted for multiple comparisons.
us adverse events, mainly brady-
ension, some of which led to
were reported more frequently
omidine sedation than during

andomized trials comparing
e with several conventionally
xmedetomidine was associated
ne to extubation, a higher num-
from coma or delirium, and a
of unresponsive sedation.[13-14]
vever, had several limitations,
intervention (up to 96 hours),[12]
rget sedation level,[11] targeting
edation (RASS score of −3 to 0)
commended,[13] a relatively short
nent, and lack of daily data on
[3] These trials were not powered
ality or other patient-centered

ationale for a potential benefit
line is based on experimental
ective effects against neuronal,
enal injury,[28,29] along with a re-
mmatory mediators after cardio-
ss[30] and reduced mortality in
Several studies and trials have
rtality associated with dexmed-
with other agents in patients
ng with lower rates and shorter
na and delirium,[12,16,17] both of
iated with increased mortal-
ether, these findings have pro-
for a possible mortality benefit
However, in our trial, we found
verall mortality with the use of
as compared with usual care.
ogeneity with respect to the
n mortality for an age above or

ADVERSE EVENTS

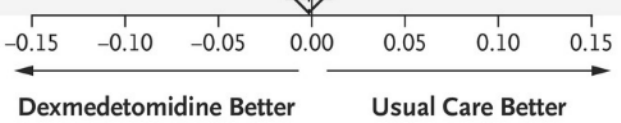
More adverse events and serious adverse events were reported in the dexmedetomidine group than in the usual-care group, most commonly bradycardia and hypotension, along with prolonged sinus arrest (asystole) (in 14 of 1954 patients [0.7%] and in 2 of 1964 patients [0.1%], respectively; P=0.003). Episodes of sinus arrest led to the administration of atropine or epinephrine or cardiac massage (in seven events) or resolved spontaneously (Table S9 in the Supplementary Appendix).

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

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*

Subgroup	Dexmedetomidine	Usual Care	Risk Difference (95% CI)
	no. of patients/total no. (%)		*percentage points*
Age			
≤Median	219/976 (22.4)	176/975 (18.1)	4.4 (0.8 to 7.9)
>Median	347/972 (35.7)	393/981 (40.1)	−4.4 (−8.7 to −0.1)
APACHE II score			
≤Median	177/977 (18.1)	204/1018 (20.0)	−1.9 (−5.4 to 1.5)
>Median	389/971 (40.1)	365/938 (38.9)	1.1 (−3.2 to 5.5)
Geographic region			
Australia and New Zealand	330/1250 (26.4)	319/1246 (25.6)	0.8 (−2.6 to 4.2)
United Kingdom and Europe	148/428 (34.6)	155/430 (36.0)	−1.5 (−7.9 to 4.9)
Malaysia	50/171 (29.2)	57/176 (32.4)	−3.1 (−12.9 to 6.6)
Saudi Arabia	38/99 (38.4)	38/104 (36.5)	1.8 (−11.5 to 15.2)
Pao_2:Fio_2 ratio			
≤Median	303/881 (34.4)	290/862 (33.6)	0.8 (−3.7 to 5.2)
>Median	205/848 (24.2)	230/892 (25.8)	−1.6 (−5.7 to 2.5)
Sepsis suspected or proved			
No	157/703 (22.3)	172/706 (24.4)	−2.0 (−6.4 to 2.4)
Yes	409/1245 (32.9)	397/1250 (31.8)	1.1 (−2.6 to 4.8)
Admission type			
Nonoperative	442/1390 (31.8)	430/1389 (31.0)	0.8 (−2.6 to 4.3)
Operative	124/556 (22.3)	139/566 (24.6)	−2.3 (−7.2 to 2.7)
Overall			−0.2 (−1.4 to 1.1)



Intensive Care Med (2021) 47:455–466

Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial

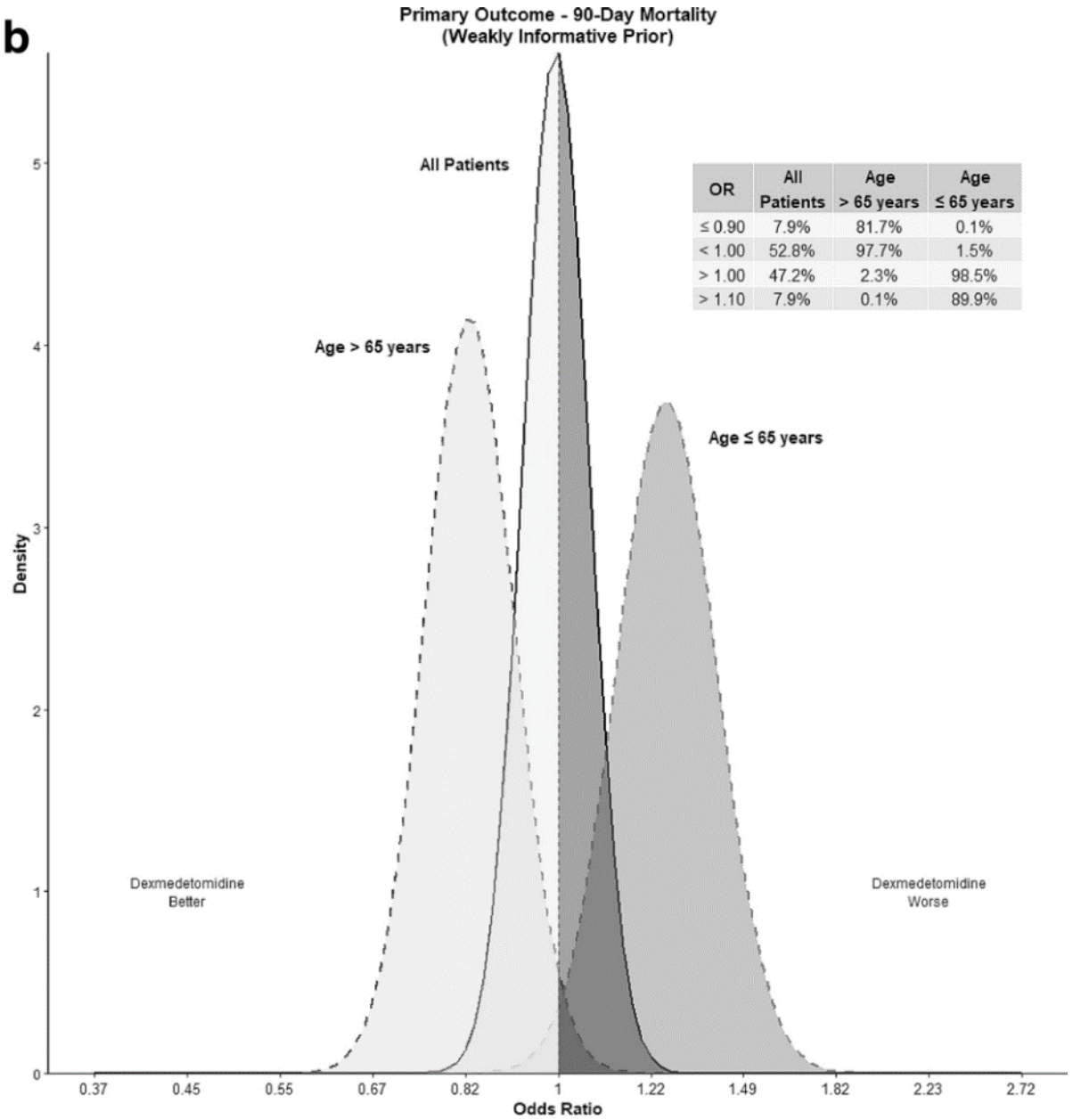
Yahya Shehabi[1,2*], Ary Serpa Neto[3,4,5,6], Belinda D. Howe[3], Rinaldo Bellomo[3,5,6], Yaseen M. Arabi[7], Michael Bailey[3,5], Frances E. Bass[8,9], Suhaini Bin Kadiman[10], Colin J. McArthur[11], Michael C. Reade[12,13], Ian M. Seppelt[14,15], Jukka Takala[16], Matt P. Wise[17] and Steve A. Webb[3,18] on behalf of The SPICE III Study Investigators

- Post-hoc analys av SPICE III-studien där man använt Bayesiansk statistik för att undersöka heterogenitet i studiematerialet
- Cut-off för ålder är 65 år
- I efteranalys har man identifierat vilka kluster (utifrån 12 baslinjekaraktäristika) där heterogenitet finns och identifierat opererad-status som faktor
- 976 patienter var opererade och 2346 patienter var icke-opererade

Intensive Care Med (2021) 47:455–466

Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial

Yahya Shehabi[1,2*], Ary Serpa Neto[3,4,5,6], Belinda D. Howe[3], Rinaldo Bellomo[3,5,6], Yaseen M. Arabi[7], Michael Bailey[3,5], Frances E. Bass[8,9], Suhaini Bin Kadiman[10], Colin J. McArthur[11], Michael C. Reade[12,13], Ian M. Seppelt[14,15], Jukka Takala[16], Matt P. Wise[17] and Steve A. Webb[3,18] on behalf of The SPICE III Study Investigators



OR	All Patients	Age > 65 years	Age ≤ 65 years
≤ 0.90	7.9%	81.7%	0.1%
< 1.00	52.8%	97.7%	1.5%
> 1.00	47.2%	2.3%	98.5%
> 1.10	7.9%	0.1%	89.9%

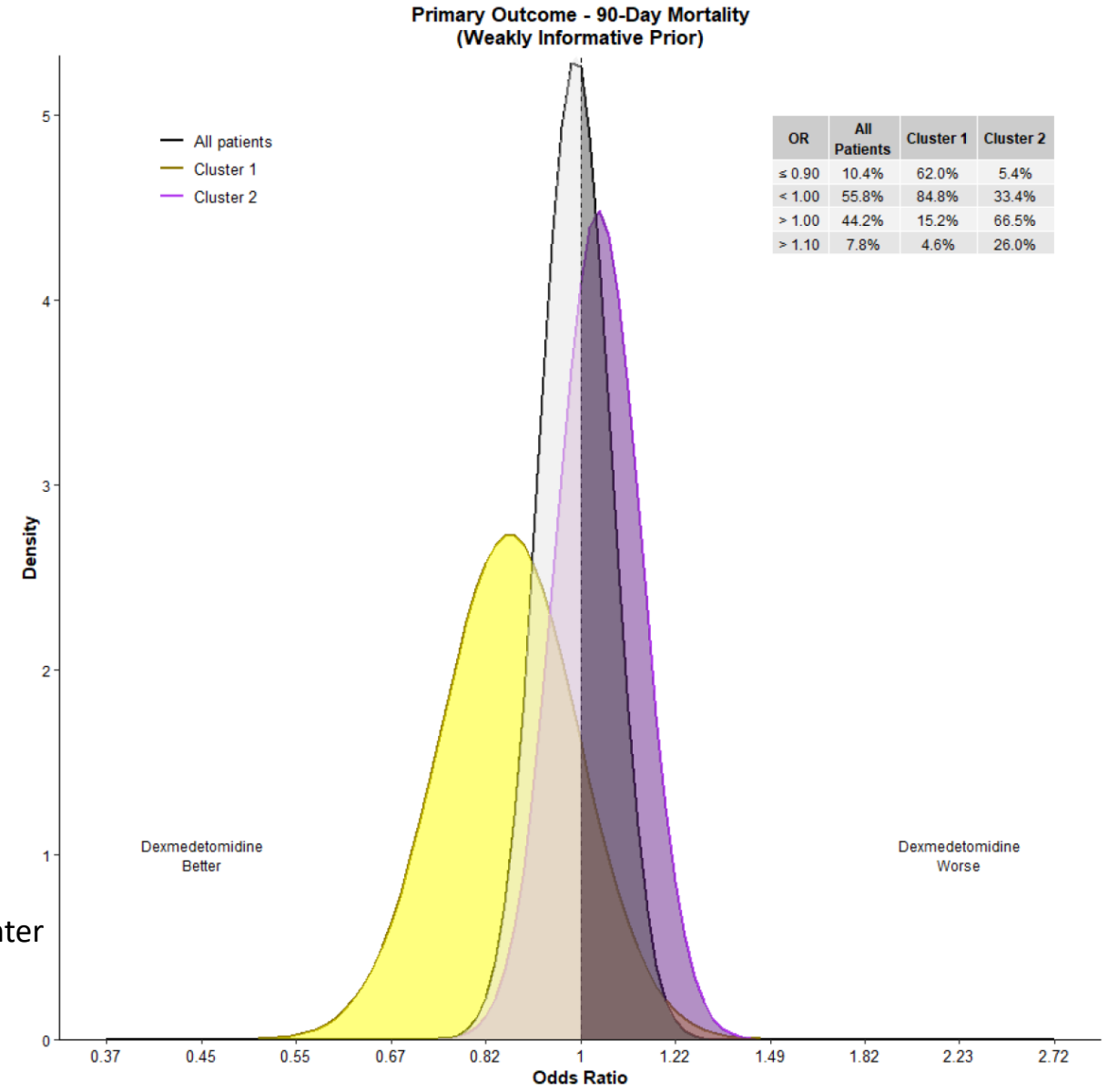
81,7% sannolikhet för att dex har en odds-ratio < 0,9 för patienter >65 åå
=dexdor är sannolikt bättre för äldre patienter i SPICE III

89,9% sannolikhet för att dex har en odds-ratio > 1,1 för patienter <65 åå
=dexdor är sannolikt sämre för yngre patienter i SPICE III

Intensive Care Med (2021) 47:455–466

Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial

Yahya Shehabi[1,2*], Ary Serpa Neto[3,4,5,6], Belinda D. Howe[3], Rinaldo Bellomo[3,5,6], Yaseen M. Arabi[7], Michael Bailey[3,5], Frances E. Bass[8,9], Suhaini Bin Kadiman[10], Colin J. McArthur[11], Michael C. Reade[12,13], Ian M. Seppelt[14,15], Jukka Takala[16], Matt P. Wise[17] and Steve A. Webb[3,18] on behalf of The SPICE III Study Investigators



OR	All Patients	Cluster 1	Cluster 2
≤ 0.90	10.4%	62.0%	5.4%
< 1.00	55.8%	84.8%	33.4%
> 1.00	44.2%	15.2%	66.5%
> 1.10	7.8%	4.6%	26.0%

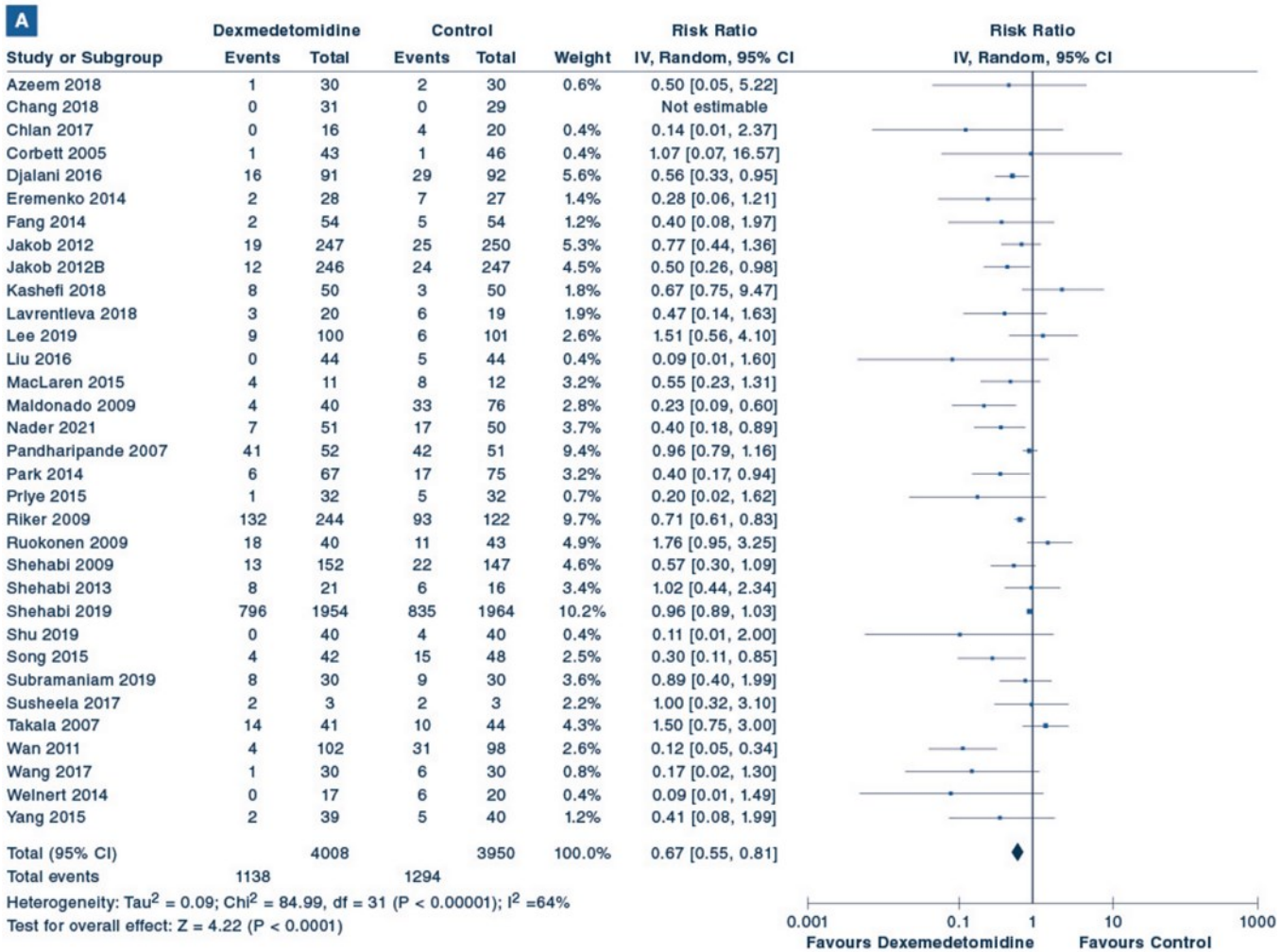
62% sannolikhet för att dex har en odds-ratio < 0,9 för opererade patienter
=dexdor är sannolikt bättre för opererade patienter i SPICE III

26% sannolikhet för att dex har en odds-ratio > 1,1 för icke-opererade patienter
=dexdor är sannolikt sämre för icke-opererade patienter i SPICE III

Intensive Care Med (2022) 48:811–840

Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials

Kimberley Lewis[1,2*], Fayez Alshamsi[3], Kallirroi Laiya Carayannopoulos[1], Anders Granholm[4], Joshua Piticaru[1], Zainab Al Duhailib[5], Dipayan Chaudhuri[1,2], Laura Spatafora[1], Yuhong Yuan[6], John Centofanti[1,7], Jessica Spence[1,2,7,8], Bram Rochwerg[1,2], Dan Perri[1,9], Dale M. Needham[10,11,12,13], Anne Holbrook[2,9], John W. Devlin[14], Osamu Nishida[15], Kimia Honarmand[16], Begüm Ergan[17], Eugenia Khorochkov[18], Pratik Pandharipande[19], Mohammed Alshahrani[20], Tim Karachi[1], Mark Soth[1], Yahya Shehabi[21], Morten Hylander Møller[4] and Waleed Alhazzani[1,2] on behalf of the GUIDE group



A

Study or Subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Azeem 2018	1	30	2	30	0.6%	0.50 [0.05, 5.22]
Chang 2018	0	31	0	29		Not estimable
Chlan 2017	0	16	4	20	0.4%	0.14 [0.01, 2.37]
Corbett 2005	1	43	1	46	0.4%	1.07 [0.07, 16.57]
Djalani 2016	16	91	29	92	5.6%	0.56 [0.33, 0.95]
Eremenko 2014	2	28	7	27	1.4%	0.28 [0.06, 1.21]
Fang 2014	2	54	5	54	1.2%	0.40 [0.08, 1.97]
Jakob 2012	19	247	25	250	5.3%	0.77 [0.44, 1.36]
Jakob 2012B	12	246	24	247	4.5%	0.50 [0.26, 0.98]
Kashefi 2018	8	50	3	50	1.8%	0.67 [0.75, 9.47]
Lavrentieva 2018	3	20	6	19	1.9%	0.47 [0.14, 1.63]
Lee 2019	9	100	6	101	2.6%	1.51 [0.56, 4.10]
Liu 2016	0	44	5	44	0.4%	0.09 [0.01, 1.60]
MacLaren 2015	4	11	8	12	3.2%	0.55 [0.23, 1.31]
Maldonado 2009	4	40	33	76	2.8%	0.23 [0.09, 0.60]
Nader 2021	7	51	17	50	3.7%	0.40 [0.18, 0.89]
Pandharipande 2007	41	52	42	51	9.4%	0.96 [0.79, 1.16]
Park 2014	6	67	17	75	3.2%	0.40 [0.17, 0.94]
Prlye 2015	1	32	5	32	0.7%	0.20 [0.02, 1.62]
Riker 2009	132	244	93	122	9.7%	0.71 [0.61, 0.83]
Ruokonen 2009	18	40	11	43	4.9%	1.76 [0.95, 3.25]
Shehabi 2009	13	152	22	147	4.6%	0.57 [0.30, 1.09]
Shehabi 2013	8	21	6	16	3.4%	1.02 [0.44, 2.34]
Shehabi 2019	796	1954	835	1964	10.2%	0.96 [0.89, 1.03]
Shu 2019	0	40	4	40	0.4%	0.11 [0.01, 2.00]
Song 2015	4	42	15	48	2.5%	0.30 [0.11, 0.85]
Subramaniam 2019	8	30	9	30	3.6%	0.89 [0.40, 1.99]
Susheela 2017	2	3	2	3	2.2%	1.00 [0.32, 3.10]
Takala 2007	14	41	10	44	4.3%	1.50 [0.75, 3.00]
Wan 2011	4	102	31	98	2.6%	0.12 [0.05, 0.34]
Wang 2017	1	30	6	30	0.8%	0.17 [0.02, 1.30]
Weinert 2014	0	17	6	20	0.4%	0.09 [0.01, 1.49]
Yang 2015	2	39	5	40	1.2%	0.41 [0.08, 1.99]
Total (95% CI)		4008		3950	100.0%	0.67 [0.55, 0.81]
Total events	1138		1294			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 84.99$, df = 31 ($P < 0.00001$); $I^2 = 64\%$

Test for overall effect: $Z = 4.22$ ($P < 0.0001$)

Risk Ratio IV, Random, 95% CI

0.001 0.1 1 10 1000

Favours Dexemedetomidine Favours Control

Intensive Care Med (2022) 48:811–840

Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials

Kimberley Lewis[1,2*], Fayez Alshamsi[3], Kallirroi Laiya Carayannopoulos[1], Anders Granholm[4], Joshua Piticaru[1], Zainab Al Duhailib[5], Dipayan Chaudhuri[1,2], Laura Spatafora[1], Yuhong Yuan[6], John Centofanti[1,7], Jessica Spence[1,2,7,8], Bram Rochwerg[1,2], Dan Perri[1,9], Dale M. Needham[10,11,12,13], Anne Holbrook[2,9], John W. Devlin[14], Osamu Nishida[15], Kimia Honarmand[16], Begüm Ergan[17], Eugenia Khorochkov[18], Pratik Pandharipande[19], Mohammed Alshahrani[20], Tim Karachi[1], Mark Soth[1], Yahya Shehabi[21], Morten Hylander Møller[4] and Waleed Alhazzani[1,2] on behalf of the GUIDE group

B

Subgroup	Dex No. Event/	Control No Patients	RR (95% CI)	RR	95% CI	I-Squared	P-Interaction
Patient type							
Cardiac Surgery	55/590	138/632		0.51	(0.38, 0.68)	0%	0.79
Medical/Surgical	24/357	61/353		0.45	(0.22, 0.96)	59%	
Patient Type							
Cardiac Surgery	55/590	138/632		0.51	(0.38, 0.68)	0%	0.76
Non-Cardiac Surgery	20/346	53/341		0.43	(0.16, 1.14)	67%	
Dose							
≤ 0.7µg/kg/h	56/785	150/832		0.46	(0.34, 0.62)	3%	N/A
> 0.7 µg/kg/h	N/A	N/A		N/A		N/A	
Duration of infusion							
≤24h	36/395	114/427		0.37	(0.21, 0.67)	50%	0.08
>24h	30/192	33/195		0.96	(040, 2.33)	72%	
Time of intiation relative to admission							
≤12h	871/2768	993/2817		0.62	(0.45, 0.84)	48%	0.22
>12h	7/62	21/67		0.36	(0.17, 0.80)	0%	
Comparator							
Propofol	48/640	104/638		0.51	(0.37, 0.71)	5%	0.03
Benzodiazapines	226/899	261/780		056	(0.40, 0.77)	72%	
Opioids	19/219	39/222		0.50	(0.30, 0.84)	0%	
Placebo	12/171	16/173		0.64	(0.19, 2.15)	65%	
Usual Care	837/2119	874/2137		1.08	(0.74, 1.57)	41%	

Intensive Care Med (2022) 48:811–840

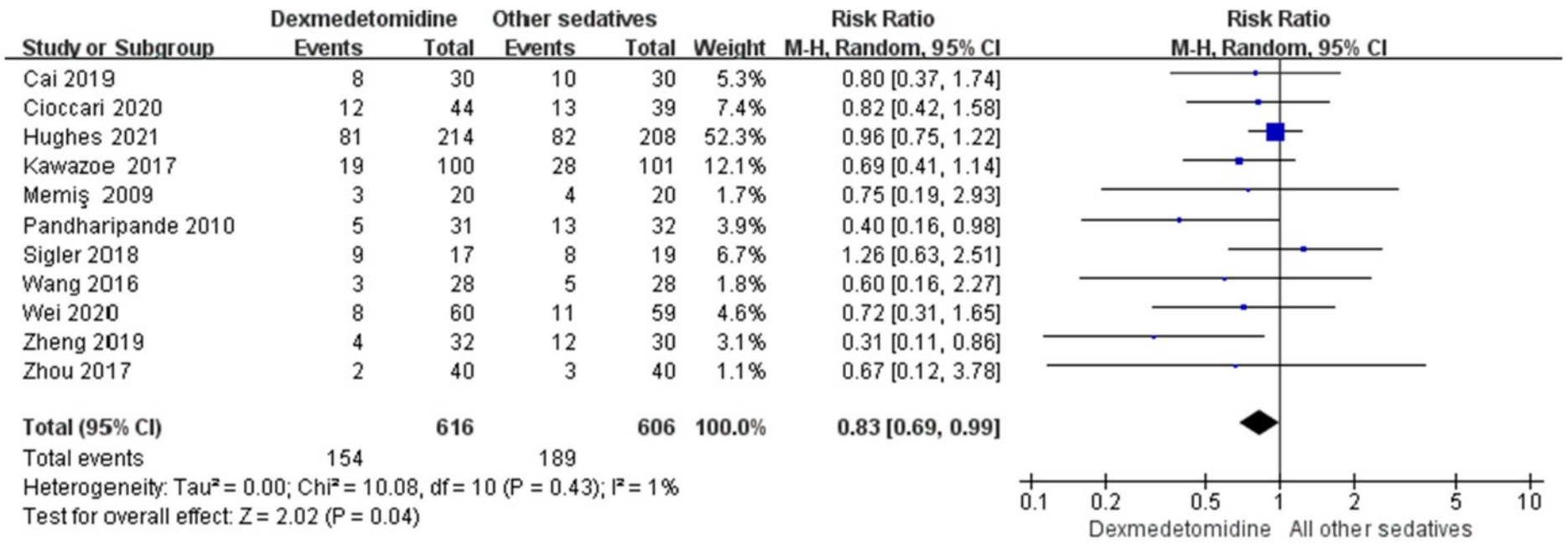
Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials

Kimberley Lewis[1,2*], Fayez Alshamsi[3], Kallirroi Laiya Carayannopoulos[1], Anders Granholm[4], Joshua Piticaru[1], Zainab Al Duhailib[5], Dipayan Chaudhuri[1,2], Laura Spatafora[1], Yuhong Yuan[6], John Centofanti[1,7], Jessica Spence[1,2,7,8], Bram Rochwerg[1,2], Dan Perri[1,9], Dale M. Needham[10,11,12,13], Anne Holbrook[2,9], John W. Devlin[14], Osamu Nishida[15], Kimia Honarmand[16], Begüm Ergan[17], Eugenia Khorochkov[18], Pratik Pandharipande[19], Mohammed Alshahrani[20], Tim Karachi[1], Mark Soth[1], Yahya Shehabi[21], Morten Hylander Møller[4] and Waleed Alhazzani[1,2] on behalf of the GUIDE group

Take-home message

In this systematic review and meta-analysis of 77 randomized clinical trials that included 11,997 patients, the use of dexmedetomidine compared to other sedation was associated with a reduction in the risk of delirium, more time at target sedation, and modest reduction in duration of mechanical ventilation and intensive care unit length of stay. However, there was an increased risk of bradycardia and hypotension.

Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials



Study or Subgroup	Dexmedetomidine Events	Total	Other sedatives Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cai 2019	8	30	10	30	5.3%	0.80 [0.37, 1.74]
Cioccari 2020	12	44	13	39	7.4%	0.82 [0.42, 1.58]
Hughes 2021	81	214	82	208	52.3%	0.96 [0.75, 1.22]
Kawazoe 2017	19	100	28	101	12.1%	0.69 [0.41, 1.14]
Memiş 2009	3	20	4	20	1.7%	0.75 [0.19, 2.93]
Pandharipande 2010	5	31	13	32	3.9%	0.40 [0.16, 0.98]
Sigler 2018	9	17	8	19	6.7%	1.26 [0.63, 2.51]
Wang 2016	3	28	5	28	1.8%	0.60 [0.16, 2.27]
Wei 2020	8	60	11	59	4.6%	0.72 [0.31, 1.65]
Zheng 2019	4	32	12	30	3.1%	0.31 [0.11, 0.86]
Zhou 2017	2	40	3	40	1.1%	0.67 [0.12, 3.78]
Total (95% CI)		**616**		**606**	**100.0%**	**0.83 [0.69, 0.99]**
Total events	154		189			

Heterogeneity: Tau² = 0.00; Chi² = 10.08, df = 10 (P = 0.43); I² = 1%
Test for overall effect: Z = 2.02 (P = 0.04)

Effect of dexmedetomidine on mortality

Zhang *et al. Annals of Intensive Care* (2022) 12:81

Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials

Conclusions

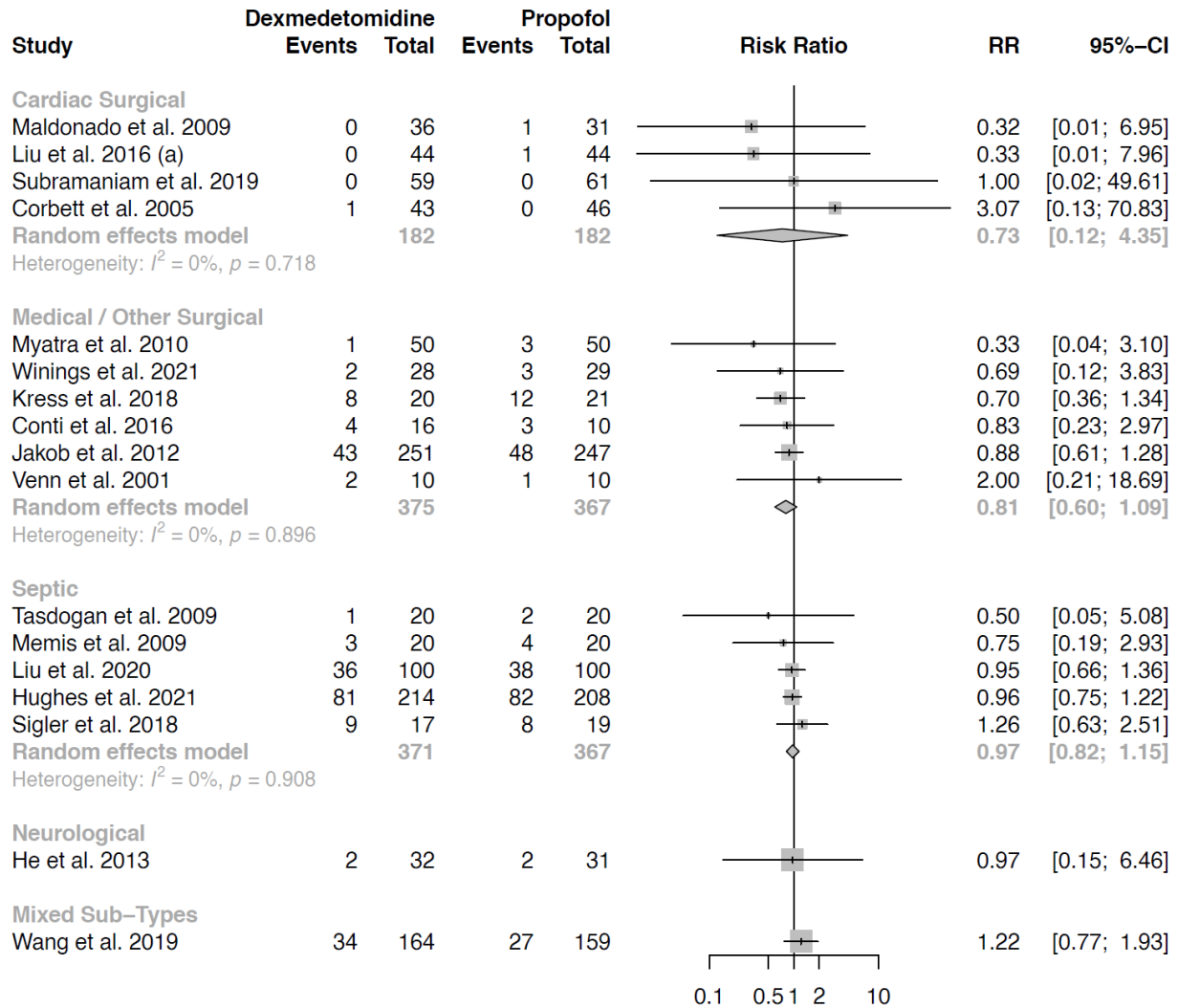
The meta-analysis showed that dexmedetomidine sedation in sepsis patients could decrease mortality compared with benzodiazepines but not with propofol. In addition, dexmedetomidine can significantly decrease inflammatory cytokine levels in sepsis patients compared with other sedatives. Dexmedetomidine might lead to an increased incidence in arrythmias, but its safety profile did not show an increased incidence of total adverse events.

British Journal of Anaesthesia, 129 (4): 515–526 (2022)

CRITICAL CARE

Outcomes of dexmedetomidine *versus* propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials

Kiyan Heybati[1,†], Fangwen Zhou[2,†], Saif Ali[2,3], Jiawen Deng[2,4], Divyanshu Mohananey[5], Pedro Villablanca[6] and Harish Ramakrishna[7,*]



Intensive Care Med (2022) 48:801–810

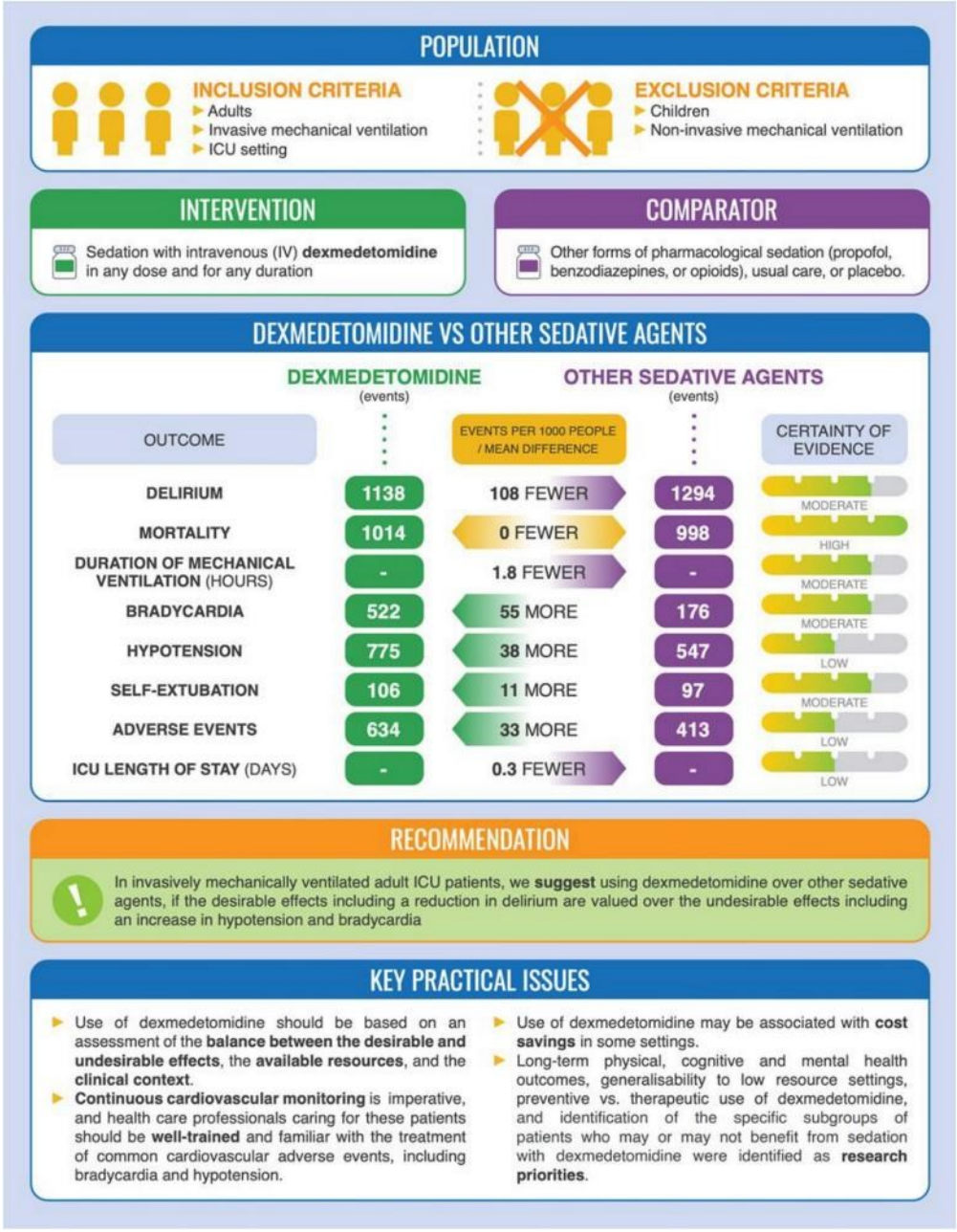
ICM RAPID PRACTICE GUIDELINES

Use of dexmedetomidine for sedation in mechanically ventilated adult ICU patients: a rapid practice guideline

Morten H. Møller[1*], Waleed Alhazzani[2,3], Kimberley Lewis[2], Emilie Belley-Cote[4], Anders Granholm[1], John Centofanti[5], William B. McIntyre[6,7], Jessica Spence[3,8], Zainab Al Duhailib[9], Dale M. Needham[10], Laura Evans[11], Annika Reintam Blaser[12,13], Margaret A. Pisani[14], Frederick D'Aragon[15,16], Manu Shankar-Hari[17], Mohammed Alshahrani[18], Giuseppe Citerio[19], Rakesh C. Arora[20], Sangeeta Mehta[21], Timothy D. Girard[22], Otavio T. Ranzani[23,24], Naomi Hammond[25,26], John W. Devlin[27,28], Yahya Shehabi[29,30], Pratik Pandharipande[31] and Marlies Ostermann[32]

Monitoring and evaluation

Given the increased risk of cardiovascular adverse events in patients receiving sedation, including in those receiving dexmedetomidine, the panel agreed that continuous cardiovascular monitoring was imperative, and that clinicians caring for these patients should be familiar with the treatment of common cardiovascular adverse effects of dexmedetomidine, including bradycardia and hypotension. The first step in the treatment is usually to reduce the infusion rate of dexmedetomidine, but this will depend on the severity of bradycardia or hypotension. Also, avoidance of boluses may reduce the risk of bradycardia.



Använd dexdor – men med förnuft

Sedering med dexmedetomidin:

- ger kortare tid i ventilator och kortare tid i delirium
- bör inte kombineras med andra sederande läkemedel
- bör inte inledas tidigt i förloppet när en ytlig sedering inte är kliniskt tillämpbar
- bör vara kort, helst <24 timmar
- dosen bör minskas vid bradykardi och helt avbrytas vid symptomgivande bradykardi

Vad vet vi efter SPICE III och efterföljande post hoc analys?

Tidig sedering med dexmedetomidin till kritiskt sjuka patienter ger:

- minskad mortalitet till patienter > 65 års ålder
- ökad mortalitet till patienter < 65 års ålder
- minskad mortalitet till opererade patienter
- ökad mortalitet till icke-opererade patienter

Mekanismen för detta är i nuläget oklar men tycks inte har cirkulatoriska orsaker

Referenser

1. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-e73.
2. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early Sedation with Dexmedetomidine in Critically Ill Patients. N Engl J Med. 2019;380(26):2506-17.
3. Shehabi Y, Serpa Neto A, Howe BD, Bellomo R, Arabi YM, Bailey M, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. Intensive Care Med. 2021;47(4):455-66.
4. Lewis K, Alshamsi F, Carayannopoulos KL, Granholm A, Piticaru J, Al Duhailib Z, et al. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. Intensive Care Med. 2022;48(7):811-40.
5. Zhang T, Mei Q, Dai S, Liu Y, Zhu H. Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials. Ann Intensive Care. 2022;12(1):81.
6. Heybati K, Zhou F, Ali S, Deng J, Mohananey D, Villablanca P, et al. Outcomes of dexmedetomidine versus propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2022;129(4):515-26.
7. Møller MH, Alhazzani W, Lewis K, Belley-Cote E, Granholm A, Centofanti J, et al. Use of dexmedetomidine for sedation in mechanically ventilated adult ICU patients: a rapid practice guideline. Intensive Care Med. 2022;48(7):801-10.