Supplementary Appendix

NCT03317067

Title : Dexmedetomidine for treatment of hyperactive delirium in non-intubated ICU patients: the 4D randomized clinical trial
Supplement to: Godet T, et al.

Version 10-27-2025

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Financial Support

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The funders had no role in the design or conduct of the study and were not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. The funding organizations do not have any ownership of the data.

Ethical considerations

The trial protocol and statistical analysis plan were approved for all centers from a central ethics committee (*Comité de Protection des Personnes Sud-Est V*, Grenoble, France; registration number 17-CHCF-02). The trial is registered in the European Clinical Trials Database (EudraCT number 2017-000731-14) and at http://www.clinicaltrials.gov with identification number NCT03317067. The trial was conducted in accordance with the tenets of the Declaration of Helsinki. The authors take responsibility for the accuracy and completeness of the data and analyses, and for the fidelity of the trial and this report to the protocol. Moreover, the first, last and third-to-last authors vouch for the fidelity of the statistical analysis plan.

Trial Inclusion Criteria

- Aged ≥ 18 years: the age of the patient in whole years at the time of randomization. The age is calculated from date of birth.
- Diagnosed delirium: delirium diagnosed by a validated screening tool, the confusion assessment method for the ICU (CAM-ICU).[1] A patient is diagnosed with delirium if the CAM-ICU assessment is positive.
- Diagnosed agitation: agitation was defined by a validated screening scale the Richmond agitation-sedation scale (RASS).[2] A patient is diagnosed with agitation if the RASS is superior or equal to +1.
- Admitted to a participating intensive care unit.

- Not intubated: non-intubation was defined as the absence of endo-tracheal intubation or tracheotomy requiring continuous positive pressure mechanical ventilation during previous 24 hours.

Trial Exclusion Criteria

- Contraindications to haloperidol: any history of intolerance to haloperidol or additives, known Parkinson disease or other extrapyramidal symptoms, known QTc prolongation, history of tardive dyskinesia, history of ventricular arrythmia or torsade de pointes, uncorrected hypokalemia (a potassium level needing action judged by clinician, only if not corrected).
- Contraindications to dexmedetomidine: any history of intolerance to dexmedetomidine or additives.
- Alcohol induced delirium/delirium tremens: delirium caused by withdrawal of alcohol after persistent alcohol use. Patients at risk were identified using Prediction of Alcohol Withdrawal Severity Scale (PAWSS ≥ 4).[3, 4]
- Recent administration of haloperidol or dexmedetomidine within previous 72 hours.
- Known severe neuropsychiatric condition.
- Permanently incompetent patient: a patient who permanently is unable to make decisions about his/her affairs (e.g. memory disorder, mental retardation). Patients may or may not have a legal guardian. The attending physician makes this assessment.
- Delirium assessment non applicable: this includes language barriers (patients with foreign language where delirium assessment cannot be confidently performed by the site staff), patients who are deaf, blind or aphasic. Comatose patients are not applicable for delirium assessment. Coma is defined by the following levels of consciousness: RASS -4 to -5. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician. If a patient's coma is considered related to administration of sedative agents, an effort should be made to reduce or terminate the sedative treatment, according to the clinician's discretion.
- Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient's charts.
- Known pregnancy: fertile women with positive urine test for human chorionic gonadotropin (hCG) or plasma-hCG.
- Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations.
- Patients under involuntary hospitalization (coercive measures) by regulatory authorities.

Consent

Due to the specific medical condition of recruited patients (hyperactive delirium), obtaining informed consent prior to participation may not be feasible, the study protocol provides for waiver of informed consent by the patient's next of kin if they are not present at the time of the patient's enrollment. Delayed

informed consent was obtained as soon as possible from participants or legally authorized surrogates for possible continuation of the research.

Screening of patients

Patients were screened for delirium and agitation at least every 4 hours during routine nursing shifts (or as clinically indicated) using the CAM-ICU and/or RASS score, respectively. Acute onset delirium (< 2 hours) was determined based on acute changes in mental status reported by nursing staff and/or family members upon ICU admission or during the current hospitalization. Patients were enrolled only if initial non-pharmacological interventions, such as reorientation, environmental adjustments, and pain control, were attempted for at least 15-30 minutes but proved insufficient to resolve symptoms or ensure patient safety.

Randomization and study medication allocation

Randomization was performed using a dedicated, password-protected, SSL-encrypted web-based system, in permuted blocks of 2, and was stratified by center to allow for immediate and concealed allocation. Study drugs (dexmedetomidine and placebo: 0.9% sodium saline) were not visually identical. However, to ensure the blinding of study drug administration, opaque reinforced envelopes were available, each containing a study drug vial (please see **Figure S1**). Trial envelopes were blinded and identified only by a unique number. Initial study drug allocation was determined by the web-based randomization system by assigning a unique envelope number. Study drug syringe preparation was performed by a nurse and/or a physician independent of the study protocol and not responsible for the enrolled patient to ensure double-blinding. These procedures aimed to prevent investigators from predicting assignments, despite the small block size. The randomization sequence was generated centrally by an independent statistician on an electronic system, and concealed within opaque, sealed envelopes accessible only to the independent compounding pharmacy/nurse, who was not involved in patient care or assessment. The small block size was chosen to ensure balance in treatment assignments early in the trial, and the strict concealment measures aimed to prevent investigators from predicting assignments. Randomization was generalized throughout all including centres rendering anticipation of next inclusion assignment unpredictable.

Additional study drug requirements (new syringe preparation) were obtained through the web-based randomization system and reassignment of a new envelope number containing an identical study drug. This ensured that patients received the study drug to which they were randomized. All personnel at the participating site and the coordinating center, with the exception of the single person who prepared the drug for administration, were blinded to the treatment allocation.

Trial Interventions

RASS was assessed hourly for the first 6 hours after randomization and then every 4 hours after enrollment; CAM-ICU was assessed at H0 and then every 12 hours; if mechanical ventilation was required, the time between enrollment and intubation was noted.

After enrollment and randomization, patients presenting with a RASS ≥ +2, received an intravenous bolus of haloperidol (2.5 mg) to promptly protect the patient from self-inflicted physical harm.[5] Indeed, dexmedetomidine requires infusion of at least 1 h to achieve full efficacy, incompatible with potentially aggressive and unsafe delirious patients.

Study Participants

The study patients were representative of patients in the participating ICUs.

Outcome Interventions

An anticipated data safety monitoring board, whose members were unaware of the treatment assignments, adjudicated all prespecified clinical outcomes (safety outcomes) in case of statistical differences.

Additional Information about Statistical Analyses

Statistical analyses were performed using Stata software (version 15, College Station, USA) and R software (version 3.3.1, R Project for Statistical Computing). Normality was assessed with the Shapiro-Wilk test and homoscedasticity with the Fisher-Snedecor test. Prespecified subgroup analyses of older patients (over 65 years of age),[6] delirium phenotype,[7] and type of admission (surgical or medical) were performed to examine the influence of each component, examining the interaction of randomization group x subgroup in regression models. If investigators or reviewers introduce analyses in addition to those described above, these will be clearly delineated as post-hoc and considered hypothesis generating.

A participant or a patient's relative who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Patients who are withdrawn from the protocol were followed up and analysed as with the remaining patients. In order to conduct intention-to-treat analyses with as little missing data as possible, it was in the interest of the trial to collect as much data from each participant as possible. Therefore, the investigators asked the participant and/or relatives which aspects of the trial they wished to withdraw from (participation in the remaining follow-up assessments or use of already collected data) and, whenever possible, the participant was asked for permission to obtain data for the primary outcome measure. If this person declined, no more data was collected, and new patients were randomized to obtain the full sample size. All randomized patients were reported, and all data available with consent were used in the analyses. If appropriate, missing data were handled in accordance with multiple imputation procedures if missing data were greater than 5% [8-10].

A sensitivity analysis was performed and the nature of missing data was studied (missing at random or not) to propose the most appropriate approach to the imputation.

Secondary Outcomes not presented in the Present Publication

The number of days with the use of physical restraints was similar between study groups (213 (31.5%) vs 235 (35.4%), absolute difference 95% CI -4 (-9 to 1), relative risk 95% CI 0.88 (0.68 to 1.16), p=0.37)

as well as the number of unexpected critical device removals (37 (48.1%) vs 45 (60.8%), absolute difference 95% CI -13 (-29 to 3), relative risk 95% CI 0.79 (0.59 to 1.06), p=0.12), between dexmedetomidine and placebo groups, respectively (**Table S5**).

Sensitivity Analysis

There was no interaction between randomization group and patient's age (p=0.996). There was no interaction between randomization group and delirium phenotype at baseline (hypoxic (p=0.689), sedative (p=0.859), septic (p=0.606), unclassified (p=0.971), despite for metabolic phenotype (p=0.012)) (**Table S6**). There was no interaction with the type of admission (p=0.406, **Table S6**).

Per-Protocol Analysis

Characteristics of per-protocol cohort are presented in **Table S7** and are similar to intention-to-treat cohort. Primary outcome was significant in the per-protocol analysis (p=0.001) (**Table S8**)**.** Similar to intention-to-treat cohort, there was no interaction between randomization group and patient's age (p=0.812). There was no interaction between randomization group and delirium phenotype at baseline (hypoxic (p=0.550), sedative (p=0.549), septic (p=0.542), unclassified (p=0.772), despite for metabolic phenotype (p=0.021)) (**Table S6**). There was no interaction with the type of admission (p=0.640, **Table S6**).

Trial Criteria for Discontinuation and Withdrawal

Studied drugs are to be used during ICU stay and for 36 hours after delirium control. Nevertheless, a participant or a patient's relative who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Patients who are withdrawn from the protocol will be followed up and analyzed as with the remaining patients. In order to conduct intention-to-treat analyses with as little missing data as possible, it is in the interest of the trial to collect as much data from each participant as possible. Therefore, the investigator may ask the participant and/or relatives which aspects of the trial they wish to withdraw from (participation in the remaining follow-up assessments or use of already collected data) and, whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. If this person declines, no more data will be collected, and new patients will be randomized to obtain the full sample size. All randomized patients will be reported, and all data available with consent will be used in the analyses.

Recruitment was stopped before the planned sample size was reached, due to the absence of safety issues and statistical significance of composite primary outcome. Using type I error correction and a statistical significance of 0.01, the trial was considered adequately powered to detect 0.5 effect-size difference between groups for primary outcome. The decision to stop enrollment was made by the investigators and the sponsor, who were unaware of the study groups. The absence of a difference in safety outcomes obviated the need to convene data safety monitoring board. Subsequent analyses show that when this decision was made, the effect estimates for the primary outcome were stable,

making it unlikely that continuing with the original sample size would have materially affected the study results.

Trial Population

Intention-to treat (ITT) population: All randomized patients except patients who withdrew consent for the use of data as stated in French law.

Per-protocol population: All randomized patients except patients having one or more major protocol violations defined as trial exclusion criteria as defined above.

- Contraindications to haloperidol: any history of intolerance to haloperidol or additives, known Parkinson disease or other extrapyramidal symptoms, known QTc prolongation, history of tardive dyskinesia, history of ventricular arrythmia or torsade de pointes, uncorrected hypokalemia (a potassium level needing action judged by clinician, only if not corrected).
- Contraindications to dexmedetomidine: any history of intolerance to dexmedetomidine or additives,
- Alcohol induced delirium/delirium tremens: delirium caused by withdrawal of alcohol after persistent alcohol use. Patients at risk were identified using Prediction of Alcohol Withdrawal Severity Scale (PAWSS ≥ 4).[3, 4]
- Recent administration of haloperidol or dexmedetomidine within previous 72 hours.
- Known severe neuropsychiatric condition.
- Permanently incompetent patient: a patient who permanently is unable to make decisions about his/her affairs (e.g. memory disorder, mental retardation). Patients may or may not have a legal guardian. The attending physician makes this assessment.
- Delirium assessment non applicable: this includes language barriers (patients with foreign language where delirium assessment cannot be confidently performed by the site staff), patients who are deaf, blind or aphasic. Comatose patients are not applicable for delirium assessment. Coma is defined by the following levels of consciousness: RASS -4 to -5. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician. If a patient's coma is considered related to administration of sedative agents, an effort should be made to reduce or terminate the sedative treatment, according to the clinician's discretion.
- Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient's charts.
- Known pregnancy: fertile women with positive urine test for human chorionic gonadotropin (hCG) or plasma-hCG.
- Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations.
- Patients under involuntary hospitalization (coercive measures) by regulatory authorities.

Handling of Missing Data

If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%. A sensitivity analysis will be performed and the nature of missing data will be studied (missing at random or not). According to this, the most appropriate approach to the imputation of missing data will be proposed.

Details on stopping rules for trial discontinuation

According to the report of DSMB provided on September 30, 2023, the conclusions were the following:

According to:
1) The results presented in this report for the primary outcome, i.e. a significant difference (P=0.001) between randomization groups with a treatment effect of -30 (-49 to -12) (3 (-23 to 51) for the group A and -27 (-45 to 10) for the group B).

2) The above-mentioned prespecified interim analysis with stopping rule criteria defined according to the Kim-DeMets correction, which suggests that a difference between the randomization groups is considered statistically significant for a type I error of 0.01.
3) Safety results described in the Clinical Outcomes table do not highlight any significant result or clinically relevant difference between groups, except use of rescue medication (P=0.003) and neuroleptics (P=0.03).

It is proposed:
1) to unblinding groups and
2) to stop enrolment at this interim analysis concluding if group B is dexmedetomidine group that in non-intubated adult ICU patients presenting with hyperactive delirium, the use of dexmedetomidine was associated with a greater clinical benefit than placebo for the composite endpoint of agitation control, delirium resolution and intubation and mechanical ventilation with safety concerns.

Figure S1. Masking of Trial Medication

The Central Pharmacy (CP) of the University Hospitals of Clermont-Ferrand (France) was responsible for the conditioning of trial medication.

Dexmedetomidine was initially bought from Orion Pharma (Dexdor® 100µg/mL, Helsinki, Finland) and then (dexmedetomidine, 100µg/mL, Ever Pharma France SAS, Lyon, France) due to a market change (generic medication).

Opaque and reinforced envelopes were produced by Clinical Pharmacologist (CP). Each envelope included study drug (either dexmedetomidine 200µg/2mL glass ampoule or placebo isotonic saline 0.9% 10 mL plastic vial), a 2 mL syringe (BD vial, Mississauga, Canada), a small gauzes package, and a 20Ga needle) to ensure study drug preparation. Fifty milliliters' syringes used to administer study drug to patients were those available at each study site.

CP was responsible for re-labelling, blinding, storage and distribution of trial medication. All services delivered by CP were performed by qualified and trained personnel and according to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). The logistics of the trial envelope's preparation and distribution to each participating centers was coordinated by the pharmacy of the coordinating center. The receipt, storage and dispensing of the blinded trial envelopes was conducted by the pharmacy department in each individual trial site.

Trial medication was contained in glass ampoules that contained 2 mL of dexmedetomidine (100µg/mL) or plastic ampoules that contained 10 mL of isotonic saline (9mg saline in sterile water).

The study drug syringes were physically compounded in a dedicated, secured preparation area within the participating ICUs by a nurse who was completely independent of the study team and direct patient care. This person was solely responsible for preparing and labelling the study medication with a unique, blinded code, ensuring that those involved in patient care, data collection, or outcome assessment remained unaware of the assigned treatment. This strict separation aimed to minimize any potential for unblinding.

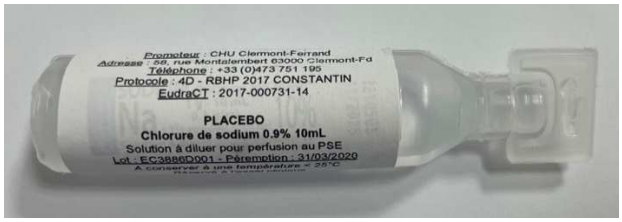
Design and disposal of opaque envelopes

Design and labeling of study drugs

Placebo:

Promoteur : CHU Clermont-Ferrand
Adresse : 58, rue Montalembert 63000 Clermont-Fd
Téléphone : +33 (0)473 751 195
Protocole : 4D - RBHP 2017 CONSTANTIN
EudraCT : 2017-000731-14

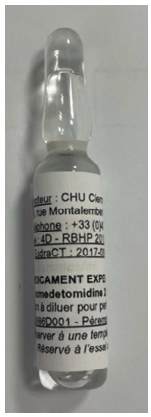
PLACEBO
Chlorure de sodium 0.9% 10mL
Solution à diluer pour perfusion au PSE
Lot : EC3886D001 - Péremption : 31/03/2020
A conserver à une température < 25°C
Réservé à l'essai clinique



Dexmedetomidine:

Promoteur : CHU Clermont-Ferrand
Adresse : 58, rue Montalembert 63000 Clermont-Fd
Téléphone : +33 (0)473 751 195
Protocole : 4D - RBHP 2017 CONSTANTIN
EudraCT : 2017-000731-14

MEDICAMENT EXPERIMENTAL
Dexmedetomidine 200µg/2mL
Solution à diluer pour perfusion au PSE
Lot : EC3886D001 - Péremption : 31/03/2020
A conserver à une température < 25°C
Réservé à l'essai clinique



Final syringe labelling:

Promoteur : CHU Clermont-Ferrand
Adresse : 58, rue Montalembert 63000 Clermont-Fd
Tél : +33 (0)473 751 195
Protocole : 4D - RBHP 2017 CONSTANTIN
EudraCT : 2017-000731-14
N° de randomisation:
Dexmédétomidine/placebo
Voie IV – Solution à perfuser en continu au PSE
A conserver à une température < 25°C
Réservé à l'essai clinique

Figure S2. Algorithm of Study Interventions

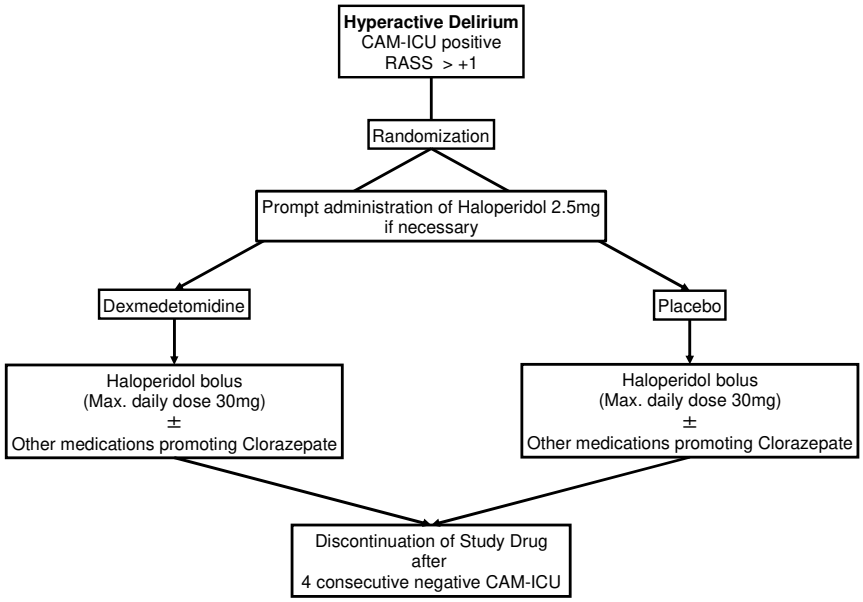


Figure S3. Distribution of Patients according to Delirium Phenotype

Venn diagram.

Delirium phenotypes have been described by Girard et al.**[7]** Several phenotypes might be identified in the same patient.

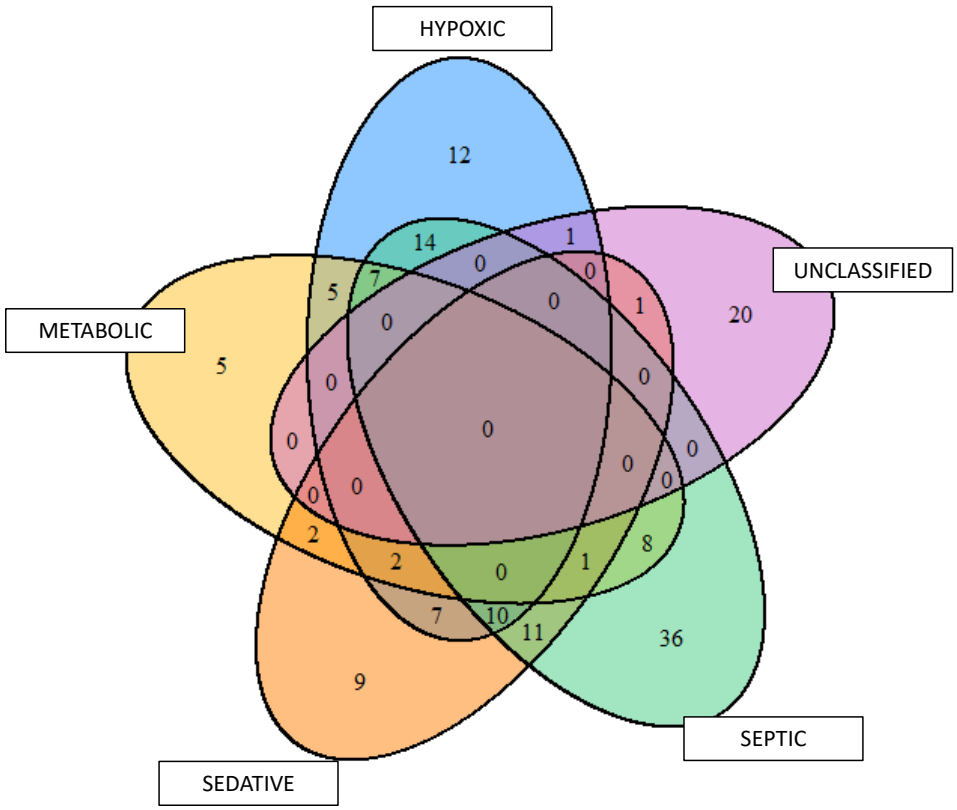
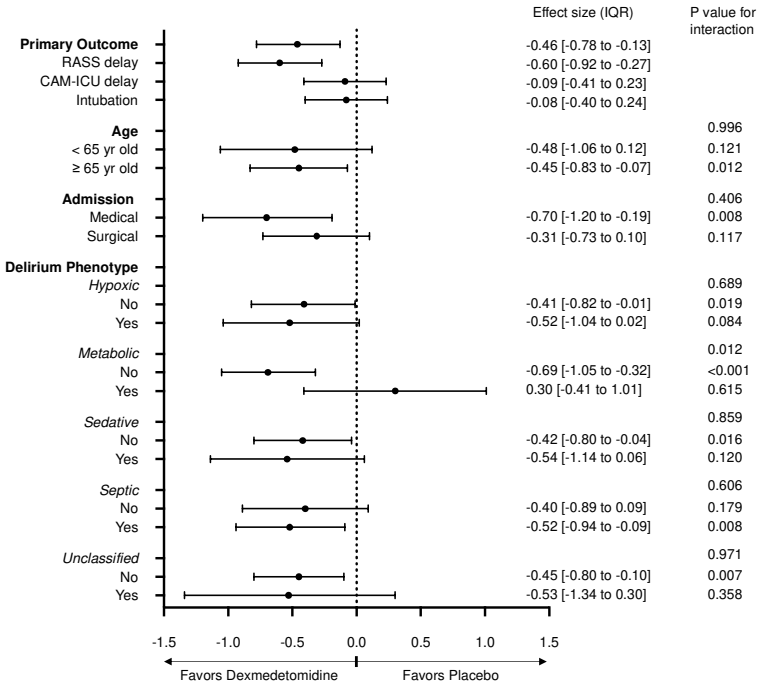
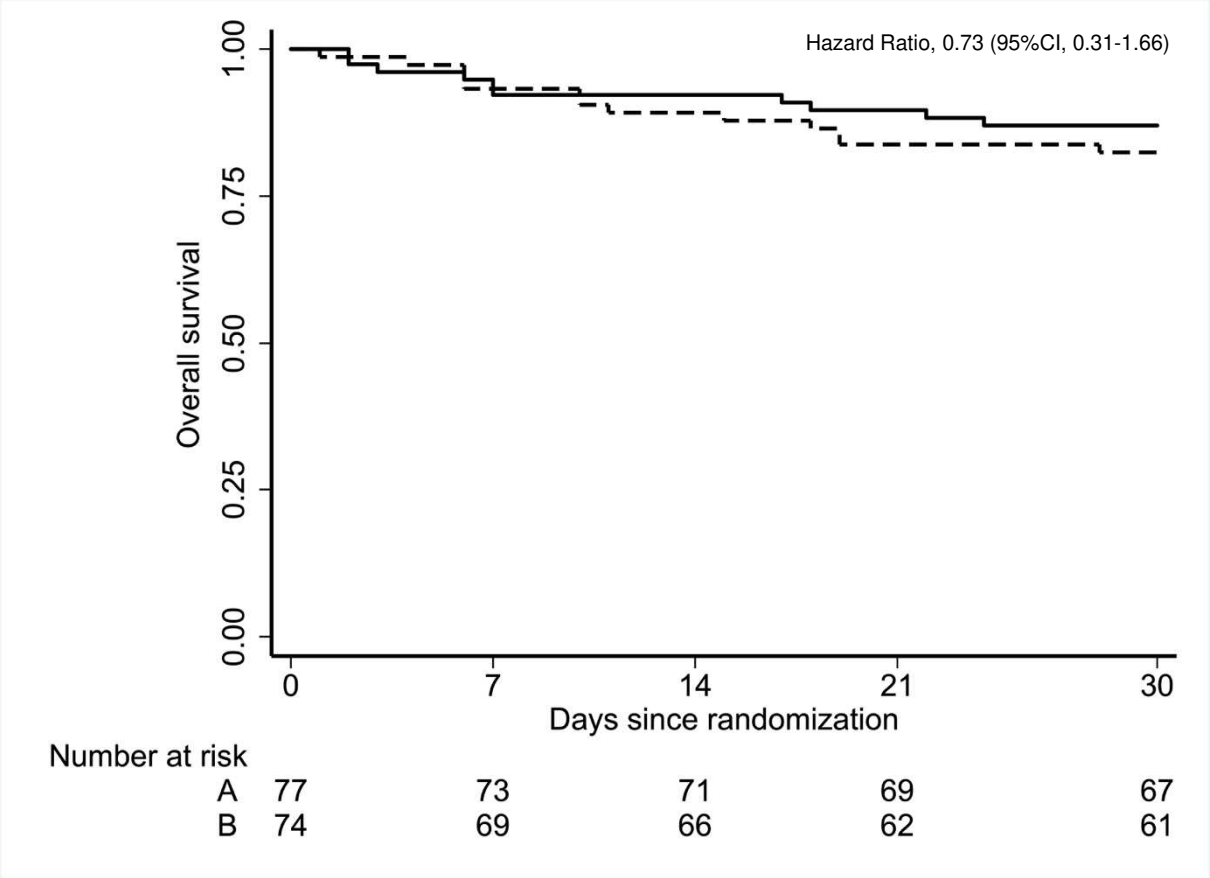


Figure S4. Effect Sizes for Primary Endpoints



P values correspond to heterogeneity of effects between groups.

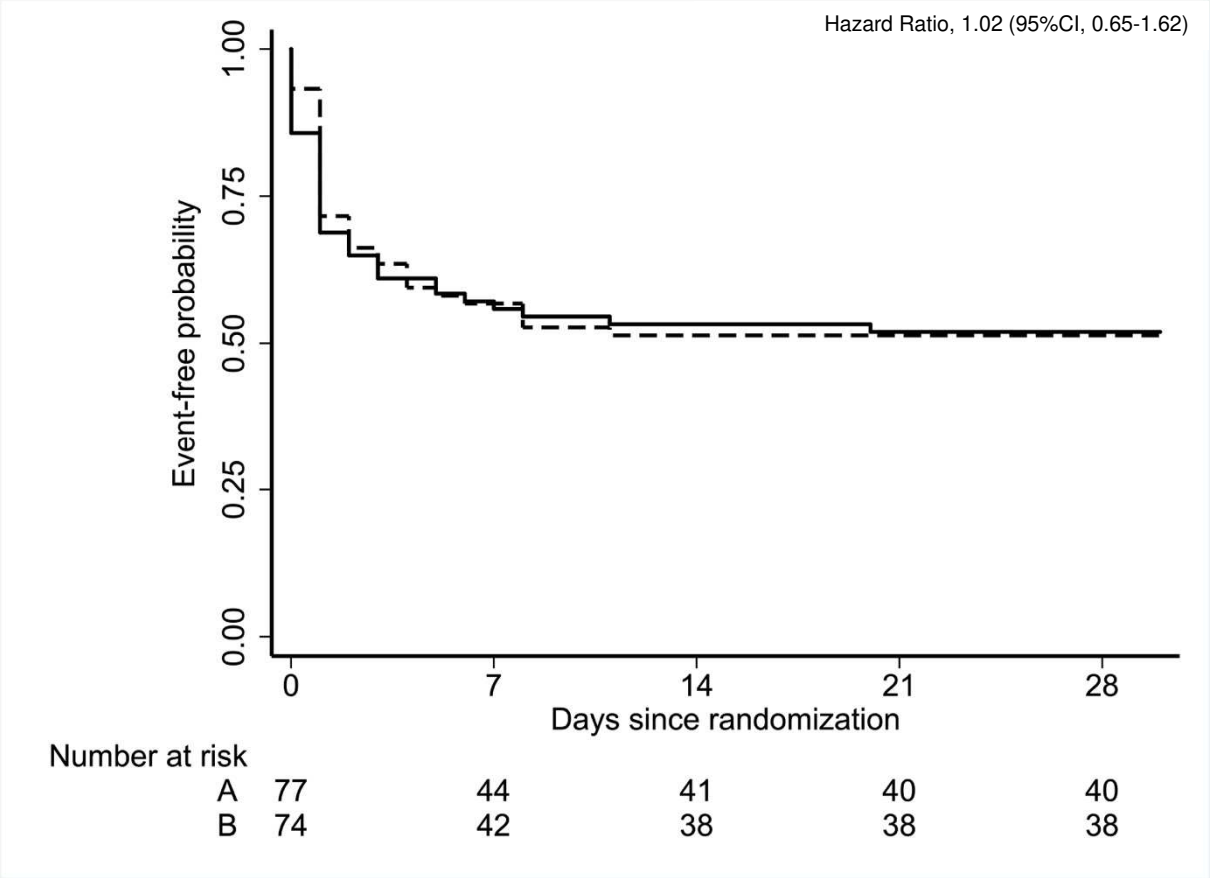
Figure S5. Kaplan-Meier curve of survival (censored at day 30)



A: dexmedetomidine group

B: placebo group

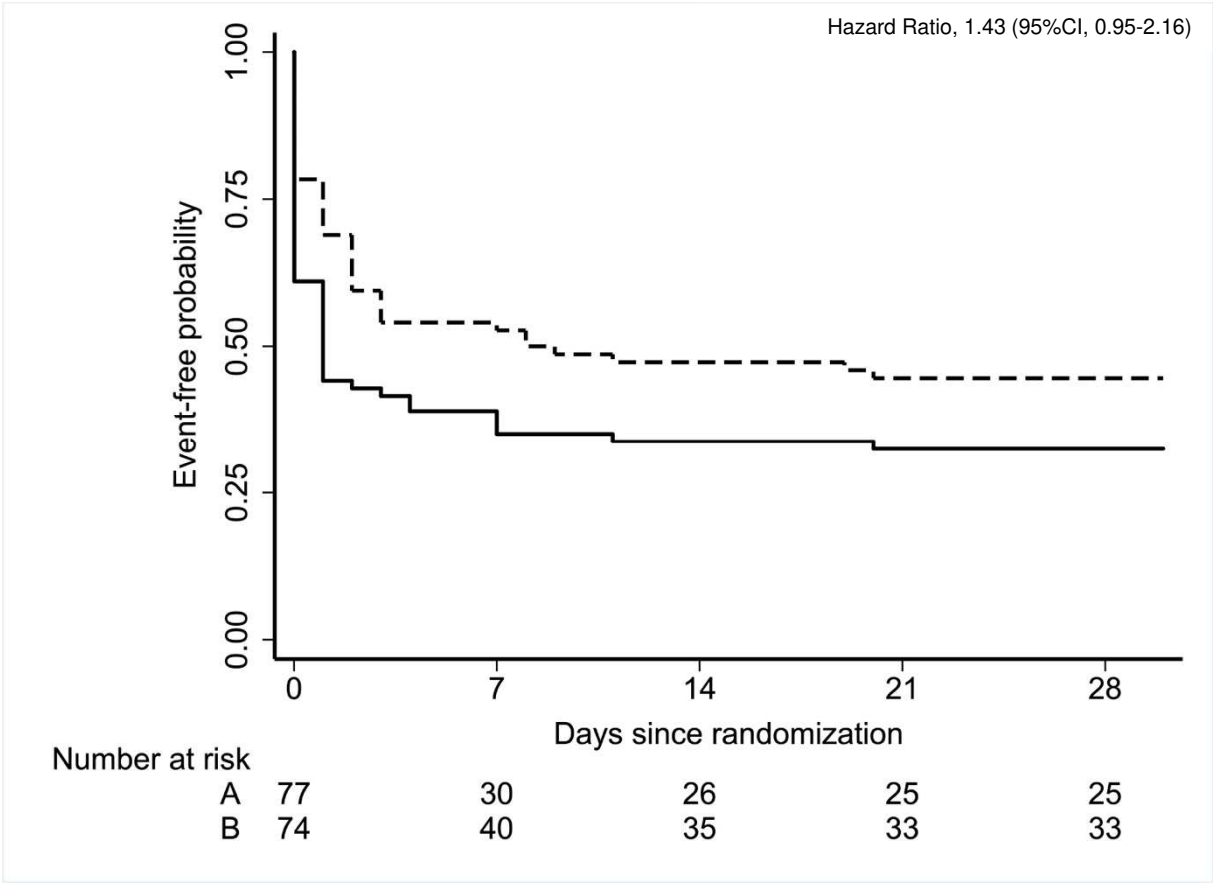
Figure S6. Kaplan-Meier curve of bradycardia (censored at day 30)



A: dexmedetomidine group

B: placebo group

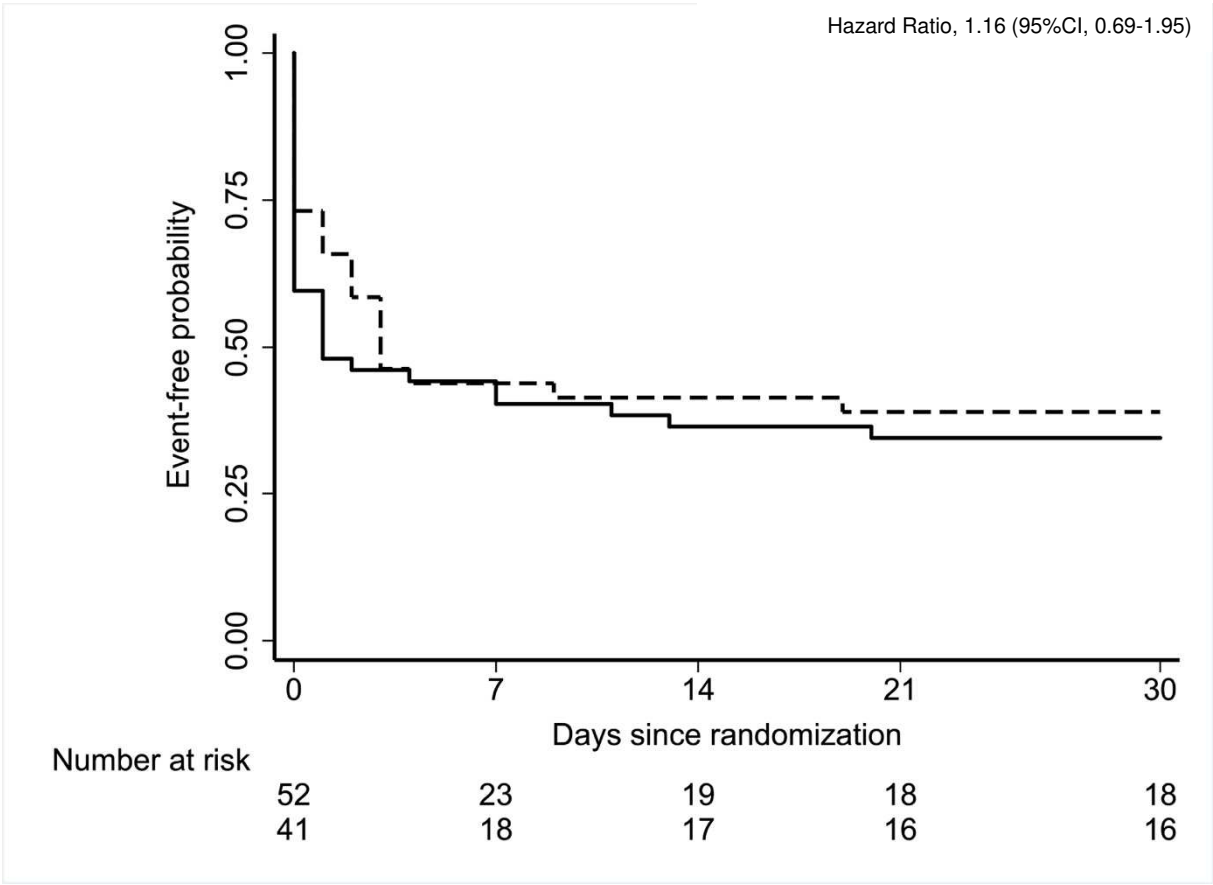
Figure S7. Kaplan-Meier curve of hypotension (censored at day 30)



A: dexmedetomidine group

B: placebo group

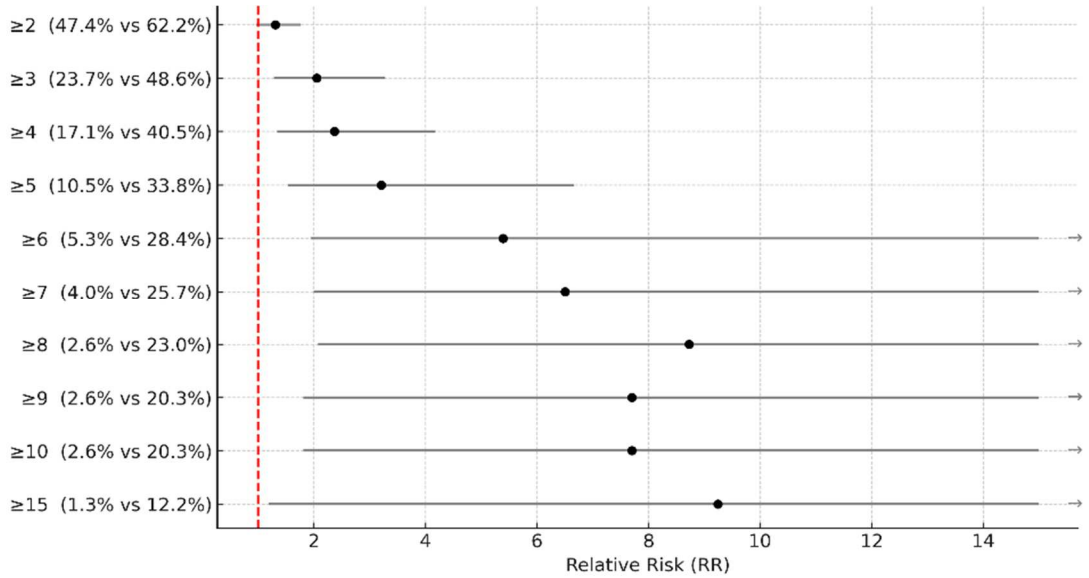
Figure S8. Kaplan-Meier curve of hypotension requiring any treatment (censored at day 30)



A: dexmedetomidine group

B: placebo group

Figure S9. Percentage of patients with persistent agitation in each randomization group and relative risks.



Each sub-group data is presented as follows: ≥ 5 (10.5% vs 33.8%) corresponding to the sub-group of patients requiring more than 5 hours to control agitation (i.e. reach a RASS < 1), that represent 10.5% of patients in dexmedetomidine group and 33.8% in placebo group.

Table S1. Details on Baseline Characteristics of Included Patients

	Placebo (N=74)	**Dexmedetomidine (N=77)**
Admission type		
Medical *	46 (62)	42 (55)
Septic shock	9 (12)	10 (13)
Hemorrhagic shock	3 (4)	3 (4)
Coma	3 (4)	4 (5)
Abdominal sepsis	6 (8)	3 (4)
Acute respiratory failure	15 (20)	15 (20)
Acute metabolic failure	8 (11)	11 (14)
Trauma	2 (3)	0
Other §	2 (3)	1 (1)
Elective surgery	15 (20)	17 (22)
Urgent surgery	13 (18)	18 (23)
Septic shock	3 (4)	4 (5)
Hemorrhagic shock	3 (4)	3 (4)
Abdominal sepsis	3 (4)	4 (5)
Acute respiratory failure	0	1 (1)
Acute metabolic failure	1 (1)	2 (2)
Trauma	3 (4)	4 (5)
Delirium phenotype # at randomization		
Hypoxic	31 (42)	27 (35)
Hypoxemia	25 (34)	22 (29)
Cardio-circulatory failure	11 (15)	7 (9)
Septic	40 (54)	47 (61)
Infection	40 (54)	47 (61)
Sedation	24 (32)	19 (25)
Benzodiazepine	14 (19)	11 (14)
Propofol	0	3 (4)
Opioids	11 (15)	8 (10)
Metabolic	13 (18)	17 (22)
Urea	13 (18)	16 (21)
Glycemia	0	1 (1)
INR	0	0
Sodium < 120 $mmol.L^{-1}$	0	0
Sodium > 160 $mmol.L^{-1}$	1 (1)	0
Unclassified	11 (15)	11 (14)

Data are presented as number (percentage).

* Several medical issues might be identified in the same patient.

§ Other include digestive occlusion in placebo group (1 (1%)) and dexmedetomidine group (1 (1%)), and cardiogenic shock in placebo group (1 (1%)).

Delirium phenotypes have been described by Girard et al.[7] Several phenotypes might be identified in the same patient (please refer to **Figure S3**).

INR denotes international normalized ratio.

Table S2. Participants Recruited per Site and Included in ITT Analysis

Site	Participants
Mixed ICU, Estaing Hospital, Clermont-Ferrand	80
Mixed ICU, Gabriel Montpied Hospital, Clermont-Ferrand	27
Mixed ICU, Montpellier University Hospital	18
Mixed ICU, Aurillac General Hospital	7
Mixed ICU, Montluçon General Hospital	4
Mixed ICU, Toulouse University Hospital	4
Neuro ICU, Gabriel Montpied Hospital, Clermont-Ferrand	3
Mixed ICU, Lyon University Hospital	3
Medical ICU, Gabriel Montpied Hospital, Clermont-Ferrand	2
Mixed ICU, Dijon University Hospital	1
Mixed ICU, Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris	1
Cardiac ICU, Grenoble University Hospital	1
Total	151

ICU denotes intensive care unit and ITT intention-to-treat.

Table S3. Time of Randomization

Number of patients randomized in the different time intervals – n (%)	**Placebo**	**Dexmedetomidine**
00:00h to 05:59h	10 (13.5)	15 (19.5)
06:00h to 11:59h	24 (32.4)	18 (23.4)
12:00h to 17:59h	29 (39.2)	26 (33.8)
18:00h to 23:59h	11 (14.9)	18 (23.4)
Randomization per weekday – n (%)		
Monday	13 (17.6)	8 (10.4)
Tuesday	15 (20.3)	16 (20.8)
Wednesday	4 (5.4)	9 (11.7)
Thursday	14 (18.9)	11 (14.3)
Friday	8 (10.8)	13 (16.9)
Saturday	13 (17.6)	9 (11.7)
Sunday	7 (9.5)	11 (14.3)

Data are presented as number (percentage).

Table S4. Characteristics of Patients according to Type of Admission

Characteristic	Medical (N=88)	Elective Surgery (N=31)	Urgent Surgery (N=32)
Median age (IQR) - years	72 (62 to 78)	69 (66 to 77)	67 (59 to 76)
Female sex	18 (21)	5 (16)	9 (28)
Median body-mass index (IQR) – $kg.m^{-2}$	27.6 (24.3 to 31.7)	26.8 (24.8 to 31.2)	26.1 (22.1 to 30.4)
Coexisting conditions			
Cardiovascular			
Hypertension	45 (51)	9 (29)	13 (41)
Dyslipidemia	17 (19)	1 (3)	4 (13)
Arteriopathy	7 (8)	8 (26)	5 (16)
Chronic cardiac failure	4 (5)	4 (13)	0
Arrythmia	18 (21)	3 (10)	6 (19)
Ischemic cardiopathy	19 (22)	7 (23)	4 (13)
Pulmonary			
COPD	19 (22)	11 (36)	6 (19)
Chronic respiratory insufficiency	3 (3)	1 (3)	2 (6)
Metabolic			
Diabetes	23 (26)	9 (29)	8 (25)
Chronic kidney injury	19 (22)	6 (19)	2 (6)
Intoxication			
Alcohol abuse	15 (17)	5 (16)	2 (6)
Tobacco	29 (30)	10 (32)	5 (16)
Drugs abuse	2 (2)	1 (3)	0
Neurology			
Cognitive impairment	5 (6)	0	0
Mild	3 (3)	NA	NA
Moderate	2 (2)	NA	NA
Neurovascular disease	5 (6)	5 (16)	3 (9)
Epilepsy	3 (3)	2 (7)	0
Chronic liver disease (cirrhosis)	5 (6)	6 (19)	1 (3)
Malignancy			
Metastatic neoplasia	3 (3)	3 (10)	1 (3)
Hematology	13 (15)	3 (10)	1 (3)
Median time from hospital admission to randomization (IQR) - days	5 (2 to 16)	7 (4 to 14)	6 (4 to 11)
Median time from ICU admission to randomization (IQR) - days	3 (2 to 9)	5 (2 to 9)	4 (3 to 7)

Median SAPS II (IQR)	41 (35 to 50)	29 (21 to 42)	39 (30 to 49)
Median predicted in-hospital mortality (IQR) – percentages	26.6 (16.7 to 46.1)	9.7 (4.2 to 28.6)	23.0 (10.6 to 43.8)
Delirium phenotype a randomization			
Hypoxic	32 (36)	27 (35)	12 (38)
Septic	50 (57)	47 (61)	20 (63)
Sedation	24 (27)	19 (25)	11 (34)
Metabolic	23 (26)	17 (22)	2 (6)
Unclassified	12 (14)	11 (14)	5 (16)
Median RASS (IQR)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)

Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage).

COPD denotes chronic obstructive pulmonary disease, ICU intensive care unit, IQR interquartile range, RASS Richmond agitation sedation scale and SAPS simplified acute physiology score.

Table S5. Additional Data to Complete Table 3 from Main Manuscript

Outcome	Placebo (N=74)	Dexmedetomidine (N=77)	Absolute Difference or Median Difference (95% CI)	Relative Risk (95% CI)	P Value
Use of physical restraints – no. (%)	58 (78.4)	56 (72.7)	-6 (-19 to 8)	0.93 (0.77 to 1.11)	0.421
Number of days with use of physical restraints – no. (%)	235 (35.4)	213 (31.5)	-4 (-9 to 1)	0.88 (0.68 to 1.16)	0.368
Unexpected device removal – no. (%)	45 (60.8)	37 (48.1)	-13 (-29 to 3)	0.79 (0.59 to 1.06)	0.120
Number of days with unexpected device removal – no. (%)	98 (14.8)	79 (11.7)	-3 (-1 to 7)	0.80 (0.53 to 1.19)	0.273
Safety (excluding Day 0 values)					
Use of open-label rescue medication	54 (73.0)	37 (46.7)	-24 (-39 to -9)	0.67 (0.51 to 0.87)	0.003
Median days with use of open-label rescue medication (54/37) (IQR)	2 (1 to 4)	4 (1 to 7)	2 (-1 to 4)	NE	0.157
Benzodiazepines	20 (51.3)	22 (81.5)	30 (9 to 52)	1.59 (1.11 to 2.27)	0.011
Median days with use of benzodiazepines as open-label rescue medication (20/22) (IQR)	1 (1 to 2)	2 (1 to 3)	1 (-1 to 2)	NE	0.217
Hydroxyzine	20 (51.3)	13 (48.2)	-3 (-28 to 21)	0.94 (0.57 to 1.55)	0.805
Median days with use of hydroxyzine as open-label rescue medication (20/13) (IQR)	3 (1 to 5)	4 (2 to 7)	1 (-2 to 4)	NE	0.251
Haloperidol	27 (36.5)	23 (30.3)	-6 (-21 to 8)	0.83 (0.53 to 1.31)	0.422
Median days with use of haloperidol as open-label rescue medication (27/23) (IQR)	1 (1 to 3)	1 (1 to 2)	-17 (-33 to -2)	NE	0.857
Neuroleptics	39 (52.7)	27 (35.5)	-17 (-33 to -2)	0.67 (0.46 to 0.98)	0.038

Median days with use of neuroleptics other than haloperidol as open-label rescue medication (39/27) (IQR)	2 (1 to 5)	4 (2 to 7)	2 (-1 to 4)	NE	0.077
Safety (including Day 0 values)					
Use of open-label rescue medication	60 (81.1)	45 (58.4)	-23 (-37 to -8)	0.72 (0.58 to 0.90)	0.003
Median days with use of open-label rescue medication (60/45) (IQR)	2 (1 to 5)	2 (1 to 6)	0 (-1 to 1)	NE	0.789
Benzodiazepines	23 (53.0)	23 (67.7)	18 (-4 to 39)	1.35 (0.93 to 1.97)	0.112
Median days with use of benzodiazepines as open-label rescue medication (23/23) (IQR)	2 (1 to 5)	4 (1 to 7)	2 (-1 to 5)	NE	0.223
Hydroxyzine	25 (54.4)	15 (44.1)	-10 (-32 to 12)	0.81 (0.51 to 1.29)	0.379
Median days with use of hydroxyzine as open-label rescue medication (25/15) (IQR)	1 (1 to 2)	1 (1 to 3)	0 (-1 to 1)	NE	0.293
Haloperidol	41 (55.4)	33 (42.9)	-13 (-28 to 3)	0.77 (0.58 to 1.08)	0.127
Median days with use of haloperidol as open-label rescue medication (41/33) (IQR)	1 (1 to 2)	1 (1 to 2)	0 (-1 to 1)	NE	0.586
Neuroleptics	46 (62.2)	34 (44.2)	-18 (-34 to -2)	0.71 (0.52 to 0.97)	0.030
Median days with use of neuroleptics other than haloperidol as open-label rescue medication (46/34) (IQR)	2 (1 to 5)	4 (1 to 7)	2 (-1 to 4)	NE	0.486

Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using relative risks (95% CI) for binary and categorical outcomes and with median differences (95% CI) for continuous outcomes. The absolute or median difference is given in percentage points. Confidence intervals for differences between groups for secondary outcomes are not adjusted for multiple comparisons of secondary outcomes and cannot be used to infer treatment effects.

CI denotes confidence interval and NE not estimated.

Table S6. Sensitivity Analysis

The following analyses were pre-specified in the statistical analysis plan. In the sensitivity analysis, the primary outcome was adjusted for stratification variable: age above or below 65 years old at baseline, delirium phenotype and type of admission. Results are presented for the dexmedetomidine group compared with placebo group.

CI denotes confidence interval.

	Intention-to-treat				**Per-protocol**			
Primary Outcome	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**
Age sub-group				0.996				0.812
Age < 65 yr old	-3 (-15 to 66)	-16 (-31 to 24)	-13 (-51 to 25)	0.121	1 (-15 to 67)	-16 (-29 to 19)	-20 (-58 to 19)	0.118
Age ≥ 65 yr old	6 (-34 to 48)	-31 (-49 to -1)	-35 (-60 to -10)	0.012	7 (-33 to 51)	-33 (-49 to -3)	-40 (-65 to -16)	0.003
Delirium phenotype at randomization								
Hypoxic				0.689				0.550
No	4 (-18 to 61)	-18 (-40 to 14)	-22 (-47 to -7)	0.019	6 (-16 to 61)	-21 (-40 to 12)	-29 (-56 to -1)	0.010
Yes	0 (-43 to 57)	-27 (-49 to 12)	-27 (-70 to 15)	0.084	6 (-29 to 57)	-27 (-49 to 12)	-33 (-77 to -1)	0.045
Metabolic				0.012				0.021
No	10 (-18 to 62)	-25 (-44 to 12)	-33 (-57 to -10)	<0.001	17 (-18 to 63)	-27 (-41 to 10)	-44 (-68 to -19)	<0.001
Yes	-3 (-59 to 2)	-12 (-37 to 19)	-9 (-55 to 37)	0.615	-1 (-58 to 9)	-12 (-37 to 19)	-10 (-54 to 35)	0.877
Sedative				0.859				0.549
No	0 (-29 to 48)	-22 (-46 to 14)	-22 (-41 to -2)	0.016	1 (-26 to 50)	-22 (-44 to 12)	-23 (-42 to -4)	0.012
Yes	9 (-37 to 67)	-21 (-38 to 12)	-31 (-82 to 21)	0.120	10 (-18 to 69)	-21 (-38 to 12)	-32 (-79 to -1)	0.042
Septic				0.606				0.542
No	1 (-33 to 35)	-21 (-49 to 24)	-22 (-58 to 14)	0.179	2 (-31 to 43)	-21 (-47 to 18)	-25 (-57 to 7)	0.127
Yes	13 (-17 to 62)	-21 (-40 to 12)	-41 (-70 to -12)	0.008	20 (-16 to 62)	-22 (-40 to 10)	-41 (-71 to -11)	0.003

Unclassified				0.971				0.772
No	4 (-18 to 62)	-20 (-40 to 14)	-23 (-46 to -1)	0.007	7 (-16 to 62)	-21 (-40 to 12)	-28 (-51 to -6)	0.001
Yes	-4 (-56 to 35)	-46 (-54 to -1)	-42 (-105 to 21)	0.358	-4 (-56 to 35)	-46 (-51 to -16)	-42 (-99 to 15)	0.403
Type of admission				0.406				0.640
Medical	8 (-14 to 59)	-23 (-46 to 14)	-33 (-67 to -1)	0.008	10 (-13 to 61)	-23 (-41 to 14)	-33 (-65 to -2)	0.007
Surgical	0 (-35 to 47)	-16 (-40 to 12)	-16 (-45 to 13)	0.117	2 (-32 to 55)	-18 (-40 to 9)	-22 (-51 to -1)	0.042

Table S7. Demographic and Clinical Characteristics of Per Protocol Cohort

Six patients were excluded in the per-protocol analysis.
Three in the Placebo group
- 1 patient was considered in delirium tremens
- 1 patient was not French speaking
- 1 patient was not CAM-ICU positive at inclusion

Three in the Dexmedetomidine group
- 2 patients were not CAM-ICU positive at inclusion
- 1 patient was not agitated (RASS < +1)

Characteristic	**Placebo (n=71)**	**Dexmedetomidine (n=74)**
Median age (IQR) - yr	72 (64 to 77)	69 (63 to 77)
Female sex	17 (24)	13 (18)
Median body-mass index (IQR) – $kg.m^{-2}$	26.0 (23.4 to 29.8)	27.7 (24.2 to 33.3)
Coexisting conditions		
Cardiovascular		
Hypertension	37 (52)	28 (38)
Dyslipidemia	10 (14)	12 (16)
Arteriopathy	10 (14)	10 (14)
Chronic cardiac failure	1 (1)	7 (9)
Arrythmia	12 (17)	14 (19)
Ischemic cardiopathy	12 (17)	18 (24)
Pulmonary		
COPD	15 (21)	21 (28)
Chronic respiratory insufficiency	3 (4)	3 (4)
Metabolic		
Diabetes	17 (24)	20 (27)
Chronic kidney injury	12 (17)	14 (19)
Intoxication		
Alcohol abuse	10 (14)	11 (15)
Tobacco	19 (27)	22 (30)
Drugs abuse	3 (4)	0
Neurology		
Cognitive impairment	3 (4)	2 (3)
Mild	2 (3)	1 (1)
Moderate	1 (1)	1 (1)
Neurovascular disease	6 (8)	6 (8)
Epilepsy	3 (4)	2 (3)

Chronic liver disease (cirrhosis)	6 (8)	5 (7)
Malignancy		
Metastatic neoplasia	3 (4)	3 (4)
Hematology	7 (10)	10 (14)
Median time from hospital admission to randomization (IQR) - days	6 (3 to 14)	6 (3 to 14)
Median time from ICU admission to randomization (IQR) - days	4 (2 to 8)	4 (2 to 9)
Admission type		
Medical	44 (62)	40 (54)
Elective surgery	14 (19)	17 (23)
Unplanned surgery	13 (18)	17 (23)
SAPS II (IQR) §	40 (32 to 47)	38 (29 to 49)
Predicted in-hospital mortality (IQR) – SAPS II (%) $	24.7 (12.8 to 39.2)	21.3 (9.7 to 43.8)
Delirium phenotype a randomization †		
Hypoxic	29 (41)	27 (37)
Septic	39 (55)	46 (62)
Sedation	23 (32)	18 (24)
Metabolic	12 (17)	17 (23)
Unclassified	11 (16)	9 (12)
Median Richmond agitation sedation scale (IQR)	1 (1 to 2)	1 (1 to 2)

Data are presented as median and 25^{th} – 75^{th} percentiles (interquartile range) or number (percentage). Characteristics listed are available baseline data for patients in the two groups who did not withdraw consent. There were no significant differences in baseline characteristics between the trial groups. No data was missing for patients at baseline.

§ The Simplified Acute Physiology Score (SAPS) II is a prediction tool for death and measures severity of disease in the ICU; scores range from 0 to 163, with higher scores indicating a greater severity of illness.[11]

$ The predicted in-hospital mortality was calculated with the use of the SAPS II, on which scores range from 0 to 163 (corresponding with a range of predicted in-hospital mortality of 0 to 100%).[11]

† Delirium phenotypes have been described by Girard et al.[7] Several phenotypes might be identified in the same patient.

* The Richmond Agitation and Sedation Scale (RASS) is a tool to assess depth of sedation on a scale of –5 to +4, with negative values denoting increased sedation and positive values denoting increased agitation.[2]

COPD denotes chronic obstructive pulmonary disease, ICU intensive care unit, IQR interquartile range, RASS Richmond agitation sedation scale and SAPS simplified acute physiology score.

Table S8. Primary Outcome in Per-Protocol Cohort

	Placebo (N=71)	**Dexmedetomidine (N=74)**	**Absolute Difference or Median Difference (95% CI)**	**Relative Risk (95% CI)**	**P Value**
Primary outcome †	5 (-23 to 61)	-21 (-40 to 12)	-27 (-46 to -8)	NE	**0.001**
Separate items					
Median delay to RASS < 1 (IQR) - hours	3.0 (1.0 to 7.0)	1.0 (1.0 to 2.0)	-2.0 (-1.0 to -3.0)	NE	**0.002**
Median delay to negative CAM-ICU (IQR) - days	1.0 (0.5 to 2.0)	1.0 (0.5 to 1.0)	0.0 (-0.5 to 0.5)	NE	0.375
Intubation – no. (%)	3 (4.2)	2 (2.7)	-1.5 (-7.5 to 4.4)	0.64 (0.11 to 3.75)	0.678

Data are presented as median and 25^{th} – 75^{th} percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using median differences (95% CI) for continuous outcomes. The absolute difference is given in percentage points for categorical outcomes. Confidence intervals for differences between groups for secondary outcomes are not adjusted for multiple comparisons of secondary outcomes and cannot be used to infer treatment effects.

† Difference between randomization groups is considered statistically significant for a type I error at 0.01 (Kim-DeMets correction), taking into account pre-planned interim analysis and primary outcome based on a composite criterion. The primary endpoint was defined as a composite score of duration of agitation (in hours), defined by a RASS ≥ +1; duration of delirium (in days), defined by a positive CAM-ICU; and requirement of intubation and mechanical ventilation related to deep sedation to control delirium. As aforementioned, the primary endpoint was calculated as suggested by O'Brien: weighted summation of single endpoints with standard procedures leads to asymptotically normal statistics. Continuous (RASS delay and CAM-ICU delay) and dichotomous (intubation) variables were converted to z-scores by subtracting an individual's value from the overall mean and dividing by the standard-deviation of the pooled group. The

z-scores were then aligned to the same direction so that worse outcomes have smaller scores. The z-scores were then averaged across endpoints for each patient. Treatment groups were compared with respect to this average z-score. The higher the value of the primary endpoint, the more unfavorable it was.

CAM-ICU confusion assessment method for the ICU, CI denotes confidence interval, ICU intensive care unit, NE not estimated and RASS Richmond agitation sedation scale.

Table S9. Details of Multivariable Analysis

The multivariable analysis was performed using a linear mixed model taking into account prespecified covariates determined according to univariate results and to clinical relevance in addition to center as a random effect.

	Mean differences (95%CI)	**P value**
Treatment, dexmedetomidine	-26 (-44 to -9)	**0.003**
Age, ≥ 65 yr old	-12 (-31 to 8)	0.206
Type of admission, medical	0 (-17 to 18)	0.958
Delirium phenotype at randomization		
Hypoxic	-13 (-32 to 7)	0.198
Metabolic	-13 (-36 to 10)	0.276
Sedative	-7 (-27 to 14)	0.522
Septic	0 (-21 to 21)	0.965
Unclassified	-35 (-67 to -3)	**0.034**

Table S10. Sensitivity Analysis (RASS score item)

	Intention-to-treat				Per-protocol			
RASS	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**
Age sub-group				0.243				0.423
Age < 65 yr old	2 (2 to 5)	1 (1 to 4)	-1 (-3 to -1)	**0.037**	3 (2 to 6)	1 (1 to 3)	-2 (-4 to -1)	**0.027**
Age ≥ 65 yr old	2 (2 to 7)	2 (1 to 2)	-1 (-2 to -1)	**0.028**	3 (1 to 8)	2 (1 to 2)	-1 (-3 to -1)	**0.020**
Delirium phenotype at randomization								
Hypoxic				0.624				0.700
No	2 (1 to 6)	2 (1 to 3)	0 (-1 to 1)	0.064	2 (1 to 6)	2 (1 to 3)	-1 (-2 to 0)	0.058
Yes	3 (1 to 8)	1 (1 to 2)	-2 (-4 to -1)	**0.010**	3 (1 to 8)	1 (1 to 2)	-2 (-4 to -1)	**0.007**
Metabolic				0.647				0.597
No	3 (1 to 8)	2 (1 to 3)	-1 (-3 to -1)	**0.004**	3 (1 to 8)	2 (1 to 3)	-1 (-2 to -1)	**0.003**
Yes	1 (1 to 2)	1 (1 to 1)	0 (-1 to 1)	0.215	1 (1 to 3)	1 (1 to 1)	0 (-1 to 1)	0.186
Sedative				0.450				0.785
No	2 (1 to 7)	1 (1 to 2)	-1 (-2 to -1)	**0.002**	2 (1 to 8)	1 (1 to 2)	-1 (-2 to -1)	**0.003**
Yes	3 (1 to 7)	2 (1 to 5)	-1 (-4 to 2)	0.654	3 (1 to 7)	2 (1 to 4)	-1 (-4 to -2)	0.356
Septic				**0.041**				**0.022**
No	2 (1 to 4)	2 (1 to 4)	0 (-2 to 2)	0.782	2 (1 to 5)	2 (1 to 5)	0 (-2 to 2)	0.876
Yes	4 (1 to 10)	1 (1 to 2)	-3 (-5 to -1)	**<0.001**	4 (1 to 10)	1 (1 to 2)	-3 (-5 to -1)	**<0.001**
Unclassified				0.624				0.453
No	3 (1 to 7)	2 (1 to 3)	-1 (-2 to -1)	**0.002**	3 (1 to 8)	1 (1 to 2)	-2 (-3 to -1)	**<0.001**
Yes	1 (1 to 5)	1 (1 to 2)	0 (-4 to 4)	0.527	1 (1 to 5)	1 (1 to 2)	0 (-4 to 4)	0.677
Type of admission				0.441				0.617
Medical	4 (2 to 10)	1 (1 to 3)	-3 (-5 to -1)	**0.005**	4 (1 to 10)	2 (1 to 3)	-2 (-4 to -1)	**0.007**
Surgical	2 (1 to 6)	1 (1 to 2)	-1 (-2 to 0)	0.090	2 (1 to 6)	1 (1 to 2)	-1 (-2 to 0)	**0.042**

Data are presented as median and 25^{th} – 75^{th} percentiles (interquartile range).

The following analyses were pre-specified in the statistical analysis plan. In the sensitivity analysis, the RASS score item was adjusted for stratification variable: age above or below 65 years old at baseline, delirium phenotype and type of admission. Results are presented for the dexmedetomidine group compared with placebo group.

Table S11. Sensitivity Analysis (CAM-ICU item)

	Intention-to-treat				Per-protocol			
CAM-ICU	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**	**Placebo**	**Dexmedetomidine**	**Treatment effect (95% CI)**	**P value**
Age sub-group				0.731				0.359
Age < 65 yr old	1.0 (0.7 to 1.6)	1.0 (0.7 to 1.9)	0.0 (-0.6 to 0.6)	0.925	1.1 (0.7 to 1.6)	1.2 (0.8 to 1.9)	0.0 (-0.7 to 0.7)	0.695
Age ≥ 65 yr old	0.9 (0.4 to 1.7)	0.7 (0.5 to 1.2)	-0.2 (-0.7 to 0.2)	0.515	1.0 (0.4 to 1.7)	0.7 (0.5 to 1.2)	-0.3 (-0.7 to 0.1)	0.270
Delirium phenotype at randomization								
Hypoxic				0.128				0.434
No	1.3 (0.6 to 1.8)	0.8 (0.5 to 1.4)	-0.5 (-0.9 to 0.1)	0.078	1.3 (0.7 to 1.8)	0.8 (0.5 to 1.4)	-0.5 (-0.9 to 0.1)	0.056
Yes	0.8 (0.3 to 1.7)	0.9 (0.6 to 1.3)	0.1 (-0.4 to 0.7)	0.245	0.8 (0.3 to 1.7)	0.9 (0.6 to 1.3)	0.1 (-0.4 to 0.7)	0.329
Metabolic				**0.016**				0.052
No	1.0 (0.5 to 1.7)	0.7 (0.5 to 1.2)	-0.3 (-0.6 to 0.1)	0.081	1.0 (0.5 to 1.7)	0.7 (0.5 to 1.2)	-0.3 (-0.6 to 0.1)	0.066
Yes	0.8 (0.5 to 1.7)	1.4 (0.8 to 1.9)	0.6 (-0.3 to 1.6)	0.102	1.0 (0.5 to 1.7)	1.4 (0.8 to 1.9)	0.3 (-0.7 to 1.2)	0.177
Sedative				**0.049**				**0.027**
No	0.9 (0.4 to 1.3)	0.9 (0.5 to 1.6)	0.0 (-0.4 to 0.4)	0.723	1.0 (0.5 to 1.5)	0.9 (0.6 to 1.6)	-0.1 (-0.4 to 0.3)	0.799
Yes	1.2 (0.5 to 2.0)	0.6 (0.5 to 1.1)	-0.6 (-1.3 to 0.0)	0.063	1.3 (0.5 to 2.0)	0.6 (0.5 to 1.1)	-0.6 (-1.3 to -0.1)	**0.031**
Septic				0.213				0.177
No	1.2 (0.5 to 1.7)	0.7 (0.5 to 1.3)	-0.5 (-1.0 to 0.1)	0.174	1.2 (0.6 to 1.7)	0.7 (0.5 to 1.3)	-0.5 (-1.0 to 0.1)	0.106
Yes	0.9 (0.5 to 1.5)	0.9 (0.5 to 1.5)	0.0 (-0.3 to 0.4)	0.724	0.9 (0.5 to 1.7)	0.9 (0.5 to 1.5)	0.0 (-0.4 to 0.4)	0.795
Unclassified				0.419				0.561
No	1.0 (0.5 to 1.7)	0.9 (0.5 to 1.4)	-0.1 (-0.4 to 0.3)	0.763	1 (0.5 to 1.7)	0.9 (0.5 to 1.4)	-0.1 (-0.5 to 0.3)	0.583
Yes	1.1 (0.5 to 1.6)	0.6 (0.5 to 1.3)	-0.5 (-1.2 to 0.3)	0.357	1.1 (0.5 to 1.6)	0.6 (0.5 to 0.8)	-0.5 (-1.1 to 0.2)	0.286
Type of admission				0.526				0.942
Medical	0.9 (0.5 to 1.3)	0.7 (0.4 to 1.1)	-0.2 (-0.1 to 0.6)	0.179	0.9 (0.6 to 1.3)	0.7 (0.4 to 1.1)	-0.2 (-0.6 to 0.1)	0.181
Surgical	1.2 (0.5 to 1.8)	1.0 (0.6 to 1.6)	-0.2 (-0.7 to 0.4)	0.900	1.2 (0.5 to 1.8)	1.0 (0.6 to 1.6)	-0.3 (-0.8 to 0.2)	0.865

Data are presented as median and 25^{th} – 75^{th} percentiles (interquartile range).

The following analyses were pre-specified in the statistical analysis plan. In the sensitivity analysis, the CAM-ICU item was adjusted for stratification variable: age above or below 65 years old at baseline, delirium phenotype and type of admission. Results are presented for the dexmedetomidine group compared with placebo group.

Table S12. Adverse reactions in pre-planned sub-groups according to age

Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using median differences (95% CI) for continuous outcomes. The absolute difference is given in percentage points for categorical outcomes. Confidence intervals for differences between groups for secondary outcomes are not adjusted for multiple comparisons of secondary outcomes and cannot be used to infer treatment effects. ICU denotes intensive care unit and NE not estimated.

a. Patients under 65

Variable	Placebo (N=21)	Dexmedetomidine (N=23)	Absolute Difference or Median Difference (95% CI)	Relative Risk (95% CI)	P Value
Serious adverse in ICU non-related to treatment - no. (%)	7 (33.3)	8 (34.8)	1 (-27 to 29)	1.04 (0.45 to 2.40)	0.919
Hypotension					
Number of patients with at least 1 episode	9 (42.9)	13 (56.5)	14 (-16 to 43)	1.32 (0.71 to 2.44)	0.365
Bradycardia					
Number of patients with at least 1 episode	8 (38.1)	8 (34.8)	-3 (-1 to 25)	0.91 (0.41 to 2.01)	0.822
Tachycardia					
Number of patients with at least 1 episode	20 (95.2)	20 (87.0)	-8 (-25 to 8)	0.91 (0.76 to 1.10)	0.609
Extrasystole					
Number of patients with at least 1 episode	0	0	NE	NE	NE
Arrythmia					
Number of patients with at least 1 episode	2 (9.5)	4 (17.4)	-8 (-12 to 28)	1.83 (0.37 to 9.13)	0.666
Cardiovascular event					
Number of patients with at least 1 episode	0 (0.0)	2 (8.7)	9 (-3 to 20)	NE	0.489

b. Patients aged 65 or over

Variable	Placebo (N=53)	Dexmedetomidine (N=54)	Absolute Difference or Median Difference (95% CI)	Relative Risk (95% CI)	P Value
Serious adverse in ICU non-related to treatment - no. (%)	20 (37.7)	18 (33.3)	-4 (23 to 14)	0.88 (0.53 to 1.48)	0.634
Hypotension					
Number of patients with at least 1 episode	32 (60.4)	39 (72.2)	12 (-6 to 30)	1.20 (0.91 to 1.57)	0.195
Bradycardia					
Number of patients with at least 1 episode	28 (52.8)	29 (53.7)	0 (-18 to 20)	1.02 (0.71 to 1.45)	0.928
Tachycardia					
Number of patients with at least 1 episode	44 (83.0)	43 (79.6)	-3 (-18 to 11)	0.96 (0.80 to 1.15)	0.653
Extrasystole					
Number of patients with at least 1 episode	8 (15.1)	6 (11.1)	-4 (-17 to 9)	0.74 (0.27 to 1.99)	0.541
Arrythmia					
Number of patients with at least 1 episode	21 (39.6)	19 (35.2)	-4 (-23 to 14)	0.89 (0.54 to 1.45)	0.635
Cardiovascular event					
Number of patients with at least 1 episode	4 (7.6)	6 (11.1)	4 (-7 to 15)	1.47 (0.44 to 4.95)	0.527

Table S13. Major Protocol Violations

Number of major protocol violations (MPVs) among patients. The count is separated by withdrawal status: patients that were withdrawn from the trial for any reason and patients that were still active in the trial (not withdrawn). MPVs were defined as:
1. Patients not receiving the allocated intervention for 2 days despite having delirium.
2. Patients receiving the allocated intervention for 2 days despite fulfilling pausing criteria (delirium free – 4 consecutive negative CAM-ICU every 12 hours).
3. Patients withdrawn from the allocated intervention despite having delirium. This includes patients discontinued from the intervention by the choice of the patient or the clinician for other reasons than SARs or SUSARs.
4. Patients receiving open-label dexmedetomidine during study period.

CAM-ICU denotes confusion assessment method for the ICU, ICU intensive care unit, SAR serious adverse event and SUSAR suspected, unexpected serious adverse reaction.

Table S14. Patients with Serious Adverse Events related to treatments pre-specified in study protocol

	Placebo	Dexmedetomidine
Total trial population	74	77
No. of patients with one or more SAE*		
Anaphylactic reaction no. (%)	0 (0.0)	0 (0.0)
Extrapyramidal Symptoms no. (%)	0 (0.0)	0 (0.0)
Neuroleptic Malignant Syndrome no. (%)	0 (0.0)	0 (0.0)
Tardive Dyskinesia no. (%)	0 (0.0)	0 (0.0)
Cardiac Arrest no. (%)	0 (0.0)	0 (0.0)

Data are presented as number (percentage).

* No patient had a serious adverse reaction.

SAE denote serious adverse events related to study treatments.

Table S15. Withdrawal and Discontinuation of the Trial Protocol

	Placebo	**Dexmedetomidine**
Total trial population that underwent randomization	**84**	**84**
Consent not given or withdrawn	7 (8.3)	10 (11.9)
Intention-to-treat population	**77**	**74**
Clinical decision	0 (0.0)	0 (0.0)
SAR or SUSAR *	0 (0.0)	0 (0.0)
QTc prolongation	0 (0.0)	0 (0.0)
Disrespect of inclusion criteria		
Not CAM-ICU positive	2 (2.6)	1 (1.4)
Not RASS > 0	1 (1.3)	0 (0.0)
Disrespect of exclusion criteria		
Chronic alcohol consumption (PAWSS > 4)	0 (0.0)	1 (1.4)
Not French speaking	0 (0.0)	1 (1.4)
Per-protocol population	**74**	**71**

Data are presented as number (percentage).

* Patients that experienced a SAR/SUSAR were only withdrawn from the trial if the SAR/SUSAR were judged related to the trial medication.

† Among patients that were withdrawn from the trial by proxy or themselves a total 17 patients did not consent to further data collection and follow-up data for the primary outcome is missing for these patients.

CAM-ICU denotes confusion assessment method for the ICU, ICU intensive care unit, PAWSS prediction of alcohol withdrawal severity scale, RASS Richmond agitation sedation scale, SAR serious adverse event and SUSAR suspected, unexpected serious adverse reaction.

Table S16. Details and Complements on Table 4 in Main Manuscript

Variable	Placebo (N=74)	Dexmedetomidine (N=77)	Absolute Difference (95% CI)	Relative Risk (95% CI)	P Value
Serious adverse event in ICU related to treatment - no. (%)	0 (0.0)	0 (0.0)	NE	NE	NE
Serious adverse event in ICU non-related to treatment - no. (%)	27 (36.5)	26 (33.8)	-3 (-18 to 13)	0.93 (0.60 to 1.43)	0.727
Hypotension					
Number of patients with at least 1 episode	41 (55.4)	52 (67.5)	12 (-3 to 28)	1.22 (0.94 to 1.58)	0.132
Number of patients requiring treatment	25/74 (33.8)	34/77 (44.2)	10 (-5 to 26)	1.31 (0.87 to 1.96)	0.198
Number of patients requiring treatment among those with at least 1 episode	25/41 (61.0)	34/52 (65.4)	4 (-15 to 24)	1.07 (0.78 to 1.47)	0.665
Number of days with at least one event during study drug administration	71/204 (34.8)	103/225 (45.8)	11 (2 to 21)	1.30 (0.88 to 1.91)	0.193
Number of days with at least one event requiring treatment	157/204 (77.0)	173/225 (76.9)	0 (-8 to 8)	1.00 (0.82 to 1.22)	0.993
Number of days with at least one event requiring treatment during study drug administration	39/71 (54.9)	69/103 (67.0)	12 (-3 to 27)	1.22 (0.84 to 1.77)	0.295
Bradycardia					
Number of patients with at least 1 episode	36 (48.7)	37 (48.1)	0 (-17 to 15)	0.99 (0.71 to 1.38)	0.942
Number of patients requiring treatment	2/74 (2.7)	3/77 (3.9)	1 (-4 to 7)	1.44 (0.25 to 8.43)	0.685
Number of patients requiring treatment among those with at least 1 episode	2/36 (5.6)	3/37 (8.1)	3 (-9 to 14)	1.46 (0.26 to 8.32)	0.670
Number of days with at least one event during study drug administration	58/131 (44.3)	59/128 (46.1)	2 (-10 to 14)	0.99 (0.62 to 1.57)	0.962
Number of days with at least one event requiring treatment	3/131 (2.3)	3/128 (2.3)	0 (-4 to 4)	1.00 (0.17 to 5.71)	0.998
Number of days with at least one event requiring treatment during study drug administration	2/58 (3.5)	1/59 (1.7)	-2 (-7 to 4)	0.49 (0.05 to 5.33)	0.559
Tachycardia					
Number of patients with at least 1 episode	64 (86.5)	63 (81.8)	-5 (-16 to 7)	0.95 (0.82 to 1.09)	0.434
Number of patients requiring treatment	13/74 (17.6)	17/77 (22.1)	5 (-8 to 17)	1.26 (0.66 to 2.40)	0.491

Number of patients requiring treatment among those with at least 1 episode	13/64 (20.3)	17/63 (27.0)	7 (-8 to 21)	1.33 (0.70 to 2.51)	0.381
Number of days with at least one event during study drug administration	177/406 (43.6)	174/449 (38.9)	-5 (-11 to 2)	0.91 (0.68 to 1.21)	0.511
Number of days with at least one event requiring treatment	47/406 (11.6)	83/449 (18.5)	7 (2 to 12)	1.27 (0.86 to 1.87)	0.222
Number of days with at least one event requiring treatment during study drug administration	9/177 (5.1)	27/174 (15.5)	10 (4 to 17)	1.32 (0.59 to 2.92)	0.500
Extrasystole					
Number of patients with at least 1 episode	8 (10.8)	6 (7.8)	-3 (-12 to 6)	0.72 (0.26 to 1.98)	0.526
Number of patients requiring treatment	2/74 (2.7)	1/77 (1.3)	-1 (-6 to 3)	0.48 (0.04 to 5.23)	0.547
Number of patients requiring treatment among those with at least 1 episode	2/8 (25.0)	1/6 (16.7)	-8 (-51 to 34)	0.67 (0.07 to 6.24)	0.722
Number of days with at least one event during study drug administration	8/15 (53.3)	2/11 (18.2)	-35 (-69 to -1)	0.32 (0.09 to 1.17)	0.085
Number of days with at least one event requiring treatment	3/15 (20.0)	1/11 (9.1)	-11 (-37 to 16)	0.42 (0.04 to 4.99)	0.494
Number of days with at least one event requiring treatment during study drug administration	1/8 (12.5)	0/2 (0.0)	-13 (-35 to 10)	NE	NE
Arrhythmia					
Number of patients with at least 1 episode	23 (31.1)	23 (29.9)	-1 (-16 to 13)	0.96 (0.59 to 1.56)	0.872
Number of patients requiring treatment	11/74 (14.9)	14/77 (18.2)	3 (-9 to 15)	1.22 (0.59 to 2.52)	0.586
Number of patients requiring treatment among those with at least 1 episode	11/23 (47.8)	14/23 (60.9)	13 (-15 to 42)	1.27 (0.74 to 2.19)	0.385
Number of days with at least one event during study drug administration	29/84 (34.5)	30/78 (38.5)	4 (-11 to 19)	1.06 (0.58 to 1.91)	0.857
Number of days with at least one event requiring treatment	31/84 (36.9)	37/78 (47.4)	11 (-5 to 26)	1.32 (0.67 to 2.59)	0.419
Number of days with at least one event requiring treatment during study drug administration	7/29 (24.1)	14/30 (46.7)	23 (-1 to 46)	1.67 (0.54 to 5.12)	0.374
Cardiovascular events #					
Number of patients with at least 1 episode	4 (5.4)	8 (10.4)	5 (-4 to 14)	1.92 (0.60 to 6.14)	0.270
Number of days with at least one event	5/58 (8.6)	23/103 (22.3)	14 (3 to 25)	2.07 (1.00 to 4.29)	0.050
Number of days with at least one event during study drug administration	1/5 (20.0)	4/23 (17.4)	-3 (-41 to 36)	0.87 (0.12 to 6.44)	0.891

Metabolic disorders					
Dyscalcemia	14 (18.9)	20 (26.0)	7 (-6 to 20)	1.37 (0.75 to 2.52)	0.305
< 1 mmol.L^{-1}	7 (9.5)	14 (18.2)	9 (-2 to 20)	1.92 (0.82 to 4.51)	0.133
> 3 mmol.L^{-1}	8 (10.8)	10 (13.0)	2 (-8 to 12)	1.20 (0.50 to 2.89)	0.682
Dysnatremia	43 (58.1)	39 (50.7)	-7 (-23 to 8)	0.87 (0.65 to 1.17)	0.360
< 135 mmol.L^{-1}	29 (39.2)	25 (32.5)	-7 (-22 to 9)	0.83 (0.54 to 1.27)	0.392
> 145 mmol.L^{-1}	21 (28.4)	21 (27.3)	-1 (-15 to 14)	0.96 (0.57 to 1.61)	0.880
Dyskaliemia	28 (37.8)	29 (37.7)	0 (-16 to 15)	1.00 (0.66 to 1.50)	0.982
< 3 mmol.L^{-1}	21 (28.4)	17 (22.1)	-6 (-20 to 8)	0.78 (0.45 to 1.36)	0.376
> 4 mmol.L^{-1}	9 (12.2)	12 (15.6)	3 (-8 to 14)	1.28 (0.57 to 2.87)	0.547

Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using median differences (95% CI) for continuous outcomes. The absolute difference is given in percentage points for categorical outcomes. Confidence intervals for differences between groups for secondary outcomes are not adjusted for multiple comparisons of secondary outcomes and cannot be used to infer treatment effects.

Cardiovascular events include the occurrence of any rhythm disorder and/or myocardial ischemia and/or tachycardia and/or hypertension and/or prolonged corrected QTc interval on the electrocardiogram. CI denotes confidence interval, ICU intensive care unit and NE not estimated

Table S17. Number of patients requiring or not haloperidol on inclusion day according to group of randomization.

	Placebo (N=74)	**Dexmedetomidine (N=77)**	**P**
Number of patients requiring haloperidol on inclusion day	30 (40.5)	18 (23.4)	**0.03**
Number of patients not requiring haloperidol on inclusion day	44 (59.5)	59 (76.6)	

Data are presented as number (percentage).

Table S18. Delays in hours to reach RASS score of 0 or below.

	Placebo (N=74)	**Dexmedetomidine (N=77)**	**P**
Patients requiring haloperidol on inclusion day	8.00 ± 8.43 5 (2 to 12)	2.61 ± 2.64 1 (1 to 3)	**< 0.001**
Patients not requiring haloperidol on inclusion day	3.98 ± 5.65 1 (1 to 4)	2.12 ± 2.70 1 (1 to 2)	

Data are presented in mean ± standard deviation and median and interquartile range.

Table S19. RASS scores at inclusion and randomization according to group.

	Placebo (N=74)	**Dexmedetomidine (N=77)**	**P**
Patients requiring haloperidol on inclusion day	1.73 ± 0.74 2 (1 to 2)	1.56 ± 0.86 1 (1 to 2)	**0.02**
Patients not requiring haloperidol on inclusion day	1.30 ± 0.51 1 (1 to 2)	1.34 ± 0.74 1 (1 to 2)	

Data are presented in mean ± standard deviation and median and interquartile range.

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