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Dexmedetomidine- or Clonidine-Based Sedation Compared With Propofol in Critically Ill Patients

The A2B Randomized Clinical Trial

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- No personal disclosures relevant to this presentation

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- Managed by the Edinburgh Clinical Trials Unit (ECTU)

Rationale and importance

Clinician Perspective

- Achieving optimum sedation (avoiding deep sedation, agitation, and delirium) is a priority
- Need for effective delirium prevention and treatments
- Current usual care is propofol (+/- opioid)
- Trend towards increasing use of alpha-2 agonists in the ICU
  - Dexmedetomidine (internationally) – licensed; more expensive
  - Clonidine (some countries) – unlicensed; inexpensive

Patient Perspective

- Optimising comfort and delirium management rated highly as clinical and research priorities
- ICU experience associated with long term mental well-being

Interventions

Dexmedetomidine

- High α2-α1 selectivity 1620:1
- Predictable kinetics
- Licensed for ICU sedation
- Widespread international use
- Ongoing uncertainty about effectiveness and safety
- Higher cost (now off-patent)

Clonidine

- Low α2-α1 selectivity 220:1
- Unpredictable kinetics
- Not licensed for ICU sedation
- Widespread use in UK (and some other countries)
- Very limited evidence-base
- Low cost

Dexmedetomidine

- Systematic reviews indicate substantial uncertainty regarding effectiveness (eg. ICM 2022 ;48(7):801-810).
  - No overall effect on mortality (high certainty)
  - V modest effects on duration of MV (low certainty)
  - Heterogeneity of effects between trials (varying populations; comparators; intervention timing; outcomes)
- SPICE III trial suggests interaction between age and mortality (NEJM 2019; 380(26):2506-17)
  - Potential mortality reduction in older patients and excess mortality in younger patients

  (ICM. 2021;47(4):455-66)
  - Current caution for dexmedetomidine use in younger ICU patients (EMA; issued June 2022)

- Typical daily cost:

  Start of trial (2018): $80-120 Current cost (off patent): $30-40

Design and setting

41 ICUs in the UK (Dec 2018- Dec 2024)

Three-arm pragmatic open-label effectiveness trial

Population: MV ICU patients within 48 hours of start of MV in ICU

Interventions:

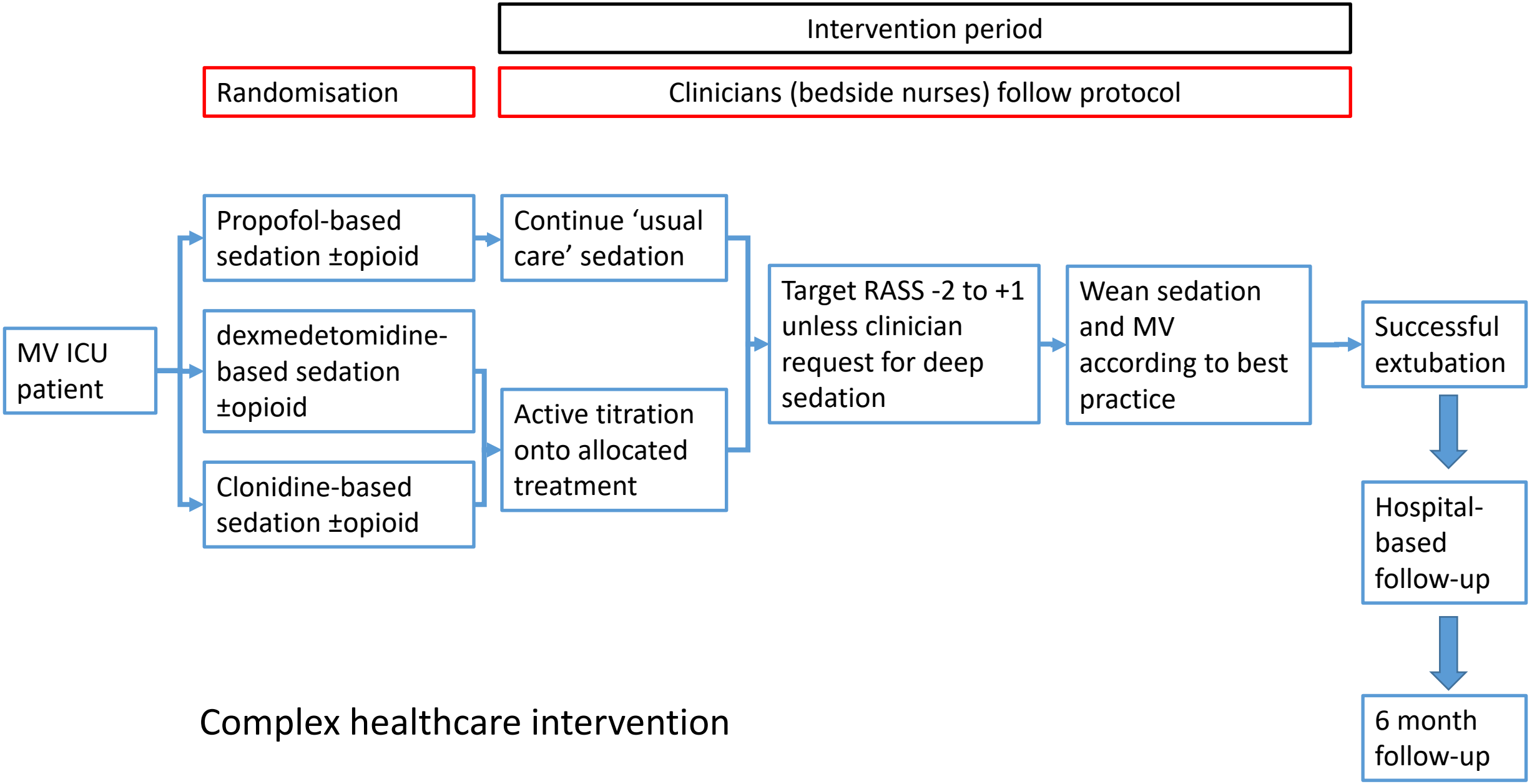
A: Clonidine-based sedation ± opioid analgesic

B: Dexmedetomidine-based sedation ± opioid analgesic

Comparator: Usual care sedation with propofol ± opioid analgesic

(Choice and use of opioid at clinical team discretion)

Primary Outcome: Time to successful extubation post-randomisation



Complex healthcare intervention

Secondary outcomes

In ICU:

Overall sedation quality (absence of pain, agitation and unnecessary deep sedation)

Time to optimum sedation

Delirium (CAM-ICU)

ICU mortality

ICU length of stay

Pre-defined drug related adverse events (severe bradycardia; cardiac arrythmia; cardiac arrest)

During 180 days follow-up:

Mortality (hospital, 30, 90, and 180 days post-randomisation)

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Secondary outcomes

In ICU:

Ability to communicate with staff and relatives

During 6 month follow-up:

Recalled experience of ICU stay (ICU experience Questionnaire - ICE-Q)

Anxiety and depression (Hospital Anxiety and Depression Scale (HADS)

Post-traumatic stress (Impact of Events Scale – Revised (IES-R)

Cognitive function (Montreal Cognitive Assessment Tool (TMoCA)

Health-related quality of life (EuroQuol - EQ-5D-5L)

Health economic evaluation

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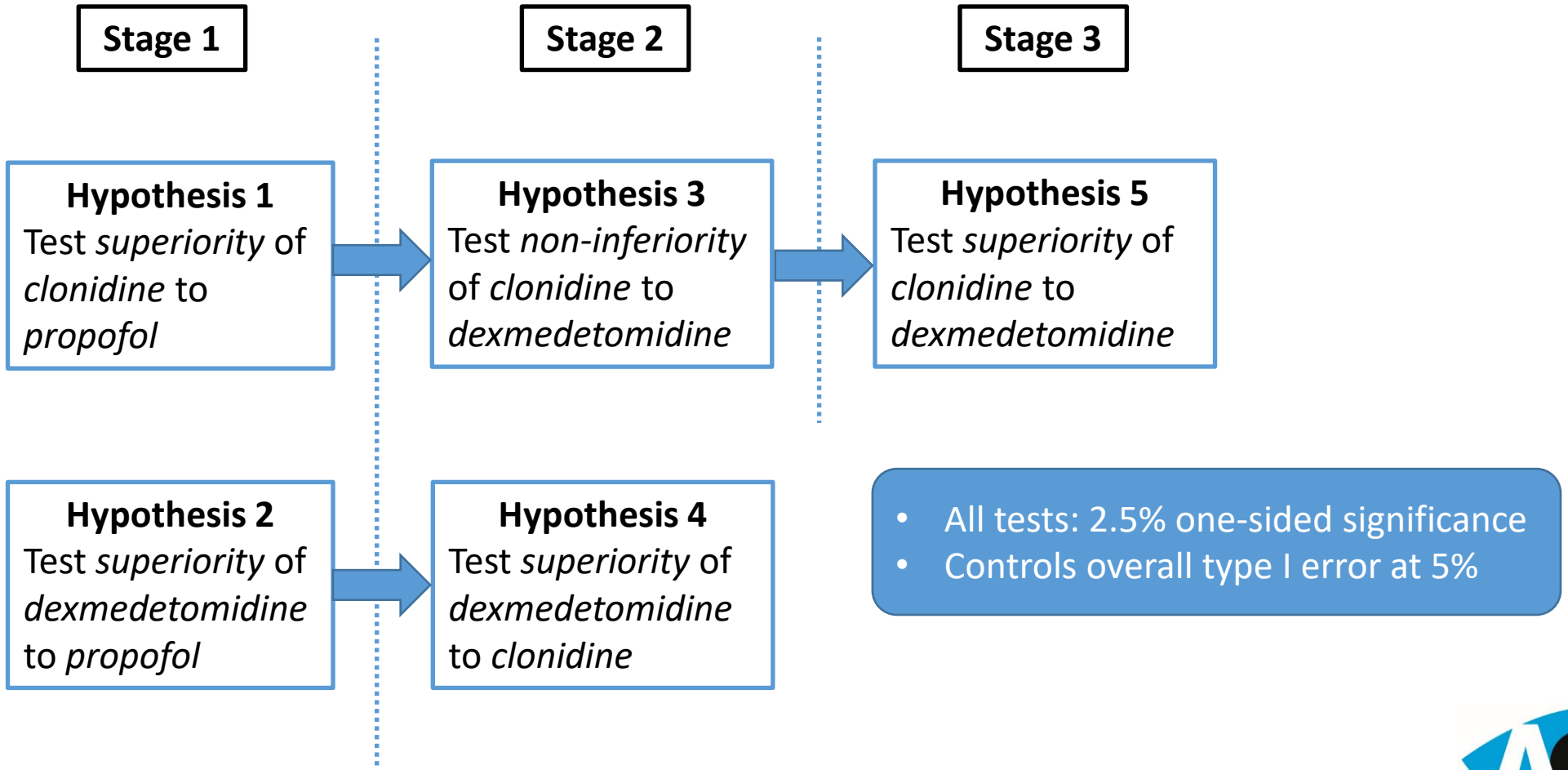
Design and sample size

Design

BMJ Open Apr 2024, 14 (4) e081637; DOI: 10.1136/bmjopen-2023-081637

See: https://doi.org/10.1136/bmjopen-2023-078645



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Sample size - Original

Assumption		Value
Event rates	7-day extubation rate	53% (from modelling of DESIST trial data 10.1016/S2213-2600(16)30178-3)
	7-day mortality rate	14% (also from DESIST)
Superiority	Significance level	2.5% one-sided
	Effect size	Mean difference 2 days in time to extubation (hazard ratio 1.37)
	Power	99%
Non-inferiority	Significance level	2.5% one-sided
	Effect size	Mean difference 1 day in time to extubation (hazard ratio 0.83)
	Power	81%
Total sample size (allowing for 5% loss to follow-up)		**1737**

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Sample size - Revised

Assumption		Value
Event rates	7-day extubation rate	53% (from modelling of DESIST trial data 10.1016/S2213-2600(16)30178-3)
	7-day mortality rate	14% (also from DESIST)
Superiority	Significance level	2.5% one-sided
	Effect size	Mean difference 2 days in time to extubation (hazard ratio 1.37)
	Power	99%
Non-inferiority	Significance level	4% one-sided
	Effect size	Mean difference 1 day in time to extubation (hazard ratio 0.83)
	Power	80%
Total sample size (allowing for 4.1% loss to follow-up)		**1437**

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Statistical modelling (1)

- Primary outcome
  - Model cumulative incidence of extubation
  - Fine & Gray (doi:10.2307/2670170) proportional sub-distribution hazards regression
  - Accounts for mortality competing risk
  - **Outputs**: sub-distribution hazard ratio, median time to extubation, absolute difference in extubation rates at 7 days
- Mortality
  - Kaplan-Meier survival curves
  - Mixed effects partially proportional hazards model adjusting for study site as a random effect
  - **Outputs**: hazard ratio
- Events of special interest

  Agitation / Unnecessary deep sedation / Pain behaviours / Delirium and coma / Severe bradycardia / Cardiac arrhythmias / Cardiac arrest
  - Poisson regression
  - Offset term for duration of follow-up; site as random effect
  - **Outputs**: rate ratio

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Statistical modelling (2)

Investigating heterogeneity of treatment effects

- Subgroup analyses
  - Presence/absence of sepsis at entry to A2B
  - PRE-DELIRIC delirium risk score above/below median
  - SOFA organ dysfunction score above/below median
  - Age <64 years / ≥64 years

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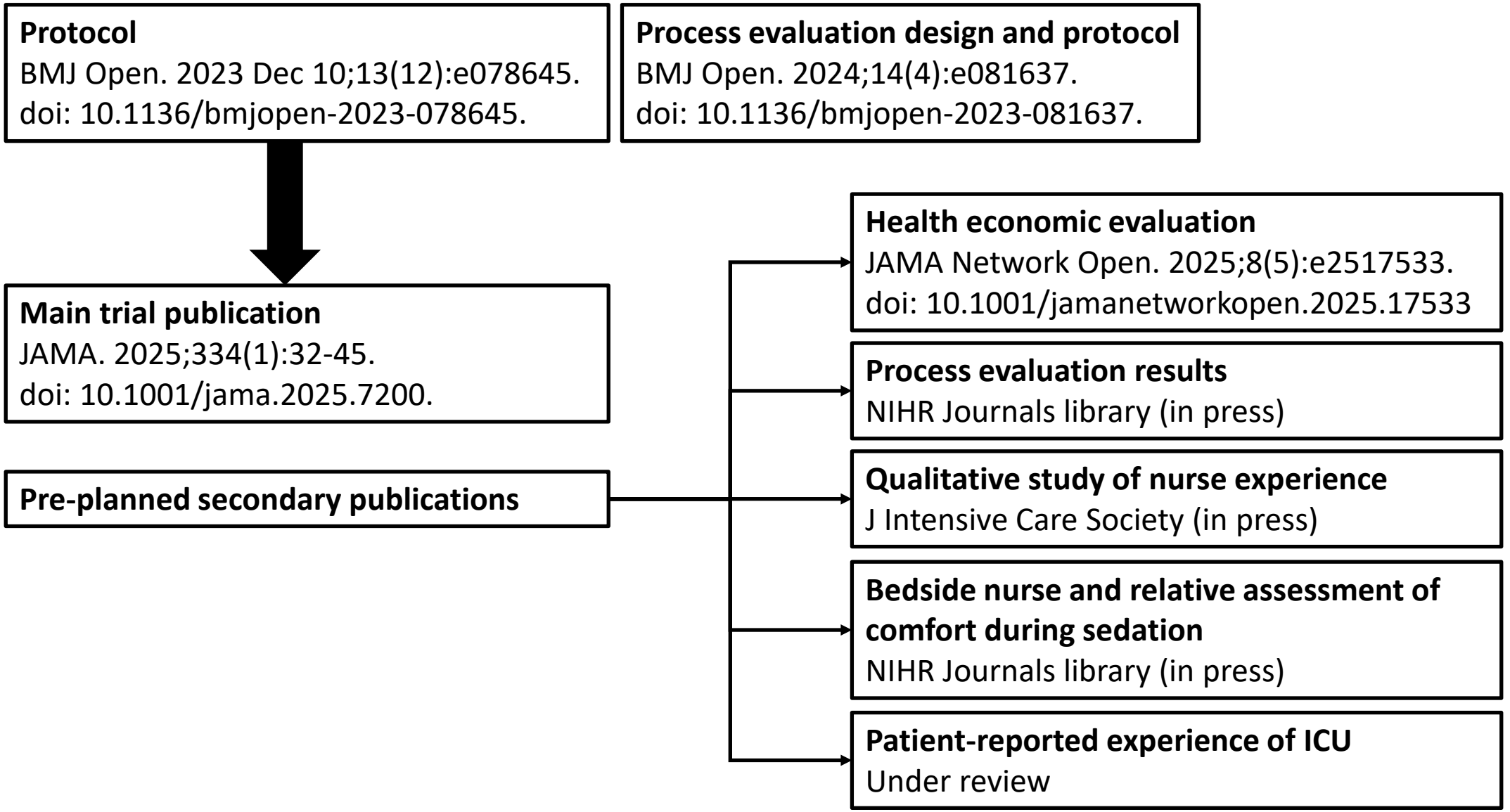
Research programme



Inclusion criteria

- Patient requiring MV in an ICU
- Aged 18 or over
- Within 48 hours of starting MV in ICU
- Requiring sedation with propofol
- Expected to require a total of 48 hours of MV or more in ICU
- Expected to require a further 24 hours of MV or more at the time of randomization in the opinion of the responsible clinician

Main exclusions primary neurological conditions

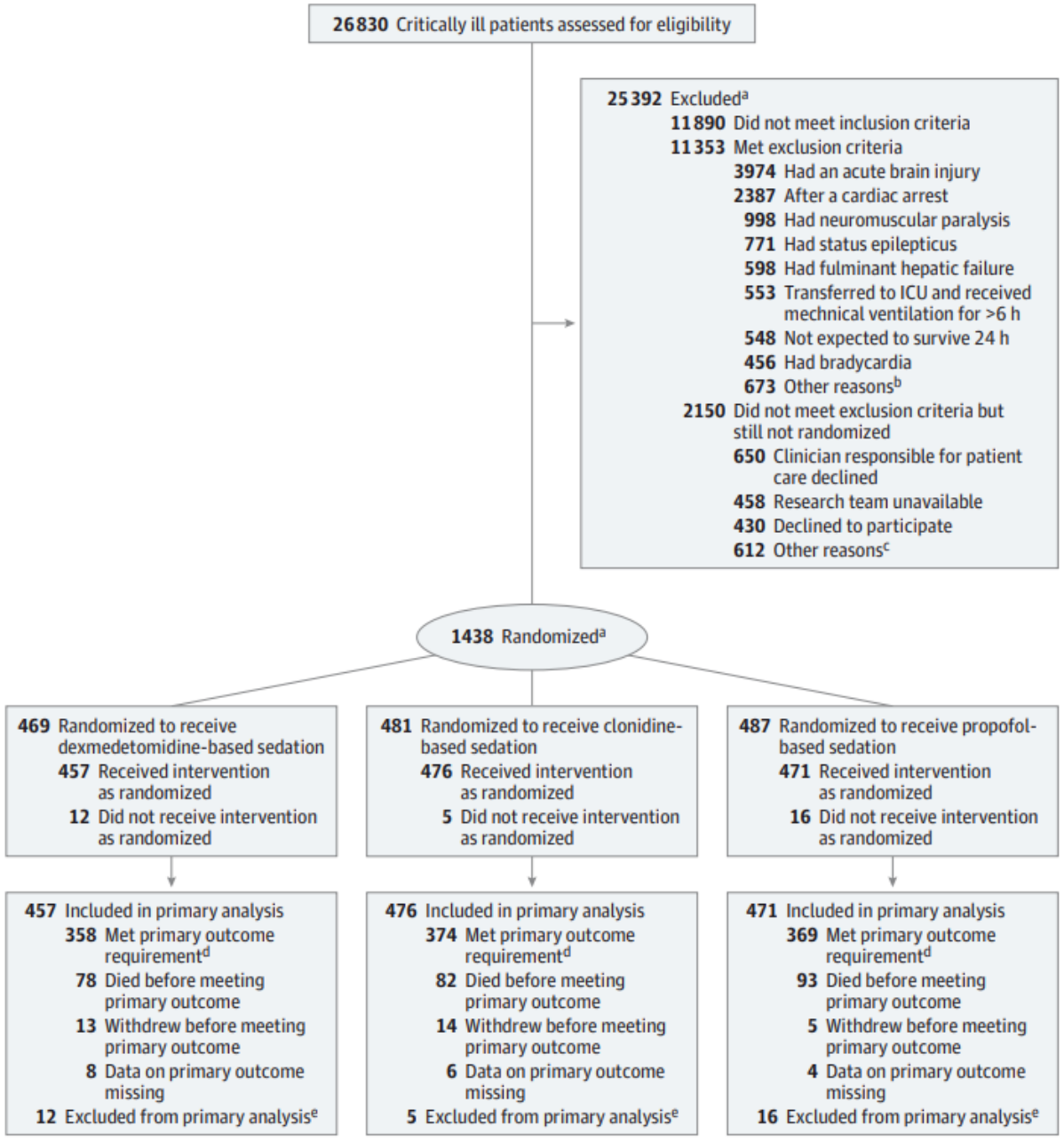
Pre-defined sub-group analyses
(baseline variables)

- **Sepsis:** Presence/absence at randomization
- **Delirium risk:** PRE-DELIRIC delirium risk score above/below median
- **Organ dysfunction:** SOFA score above/below median
- **Age:** <64 years / ≥64 years

All sub-group analyses for primary outcome

Age for mortality (including continuous effects)

Figure 1. Flow Diagram for Screening, Randomization, and Follow-Up in the Study



40% eligible patients included

Follow-up (primary outcome): 96.4%

Table 1. Baseline Characteristics for the Patients Included in the Primary Analysis Population

	Sedation group		
	Dexmedetomidine (n = 457)	Clonidine (n = 476)	Propofol (n = 471)
Age, y	(n =456)	(n = 472)	(n = 475)
Mean (SD)	58.8 (14.8)	59.6 (14.5)	59.2 (15.2)
Group, No. (%)			
18-64	287 (62.9)	272 (57.6)	268 (56.4)
65-84	164 (36.0)	193 (40.9)	203 (42.7)
≥85	5 (1.1)	7 (1.5)	4 (0.8)
Sex, No. (%)	(n =449)	(n = 469)	(n = 469)
Male	292 (65.0)	306 (65.2)	303 (64.6)
Female	157 (35.0)	163 (34.8)	166 (35.4)
Estimated weight, mean (SD), kg	(n =449) 81.7 (21.8)	(n = 469) 83.6 (22.8)	(n = 469) 81.7 (22.0)
Functional Comorbidity Index at admission, No. (%)[a]	(n =449)	(n = 469)	(n = 469)
0	121 (26.9)	115 (24.3)	119 (25.4)
1	123 (27.4)	134 (25.7)	122 (26.0)
2	97 (21.6)	103 (25.3)	120 (25.5)
≥3	108 (24.0)	117 (24.7)	108 (23.0)
APACHE II score, mean (SD)[b]	(n =449) 20.0 (8.0)	(n = 467) 20.3 (8.1)	(n = 467) 20.8 (8.5)
Time from start of mechanical ventilation in ICU to randomization, median (IQR), h	(n =457) 20.7 (12.9-31.4)	(n = 476) 21.0 (13.3-32.1)	(n = 471) 21.0 (13.4-30.5)
SOFA score, median (IQR)[c]	(n =449)	(n = 469)	(n = 469)
Respiratory	3 (2-3)	3 (2-3)	3 (2-3)
Cardiovascular	4 (3-4)	4 (3-4)	4 (3-4)
Coagulation	0 (0-1)	0 (0-1)	0 (0-1)
Kidney	1 (0-3)	1 (0-2)	1 (0-3)
Liver	0 (0-1)	0 (0-1)	0 (0-1)
Total[d]	8 (6-10)	8 (7-10)	8 (7-10)
Lactate level, mean (SD), mmol/L	(n =445) 1.7 (1.4)	(n = 468) 1.7 (1.5)	(n = 468) 1.6 (1.6)
Type of ICU admission	(n =449)	(n = 469)	(n = 469)
Medical			
Planned	10 (2)	6 (1)	9 (2)
Unplanned	271 (60)	275 (59)	286 (61)
Surgical			
Planned	23 (5)	30 (6)	27 (6)
Unplanned	112 (25)	116 (25)	117 (25)
Trauma			
Planned	5 (1)	2 (<1)	2 (<1)
Unplanned	28 (6)	40 (9)	28 (6)
Primary ICU admission diagnosis (by system)			
Cardiovascular	27 (6)	29 (7)	19 (5)
Respiratory	155 (36)	158 (36)	158 (38)
Gastrointestinal	120 (28)	108 (24)	112 (27)
Neurological	15 (4)	13 (3)	16 (4)
Other	110 (26)	133 (30)	111 (27)
Unknown	30 (7)	35 (8)	55 (13)
Sepsis status assessed, No. (%)[e]	(n =449) 297 (66.1)	(n = 469) 303 (64.6)	(n = 469) 308 (65.7)
PRE-DELIRIC (delirium) risk score, median (IQR), %[f]	(n =445) 73 (53-85)	(n = 468) 74 (55-86)	(n = 468) 72 (51-87)

Baseline population characteristics

Age (mean; SD)	59.2 (14.9)
Age <65 yrs (N; %)	827 (58.9)
APACHE II score (mean; SD)	20.3 (8.2)
MV to randomization (hours; median IQR)	21.0 (13.2, 31.3)
SOFA score (non-neurologic)	8 (7, 10)
CVS SOFA (median, IQR)	4 (3, 4)
Sepsis (N, %)	908 (65.5)
PRE-DELIRIC score (%) (median, IQR)	73 (53, 86)

Results – intervention fidelity

Exposure to each study drug

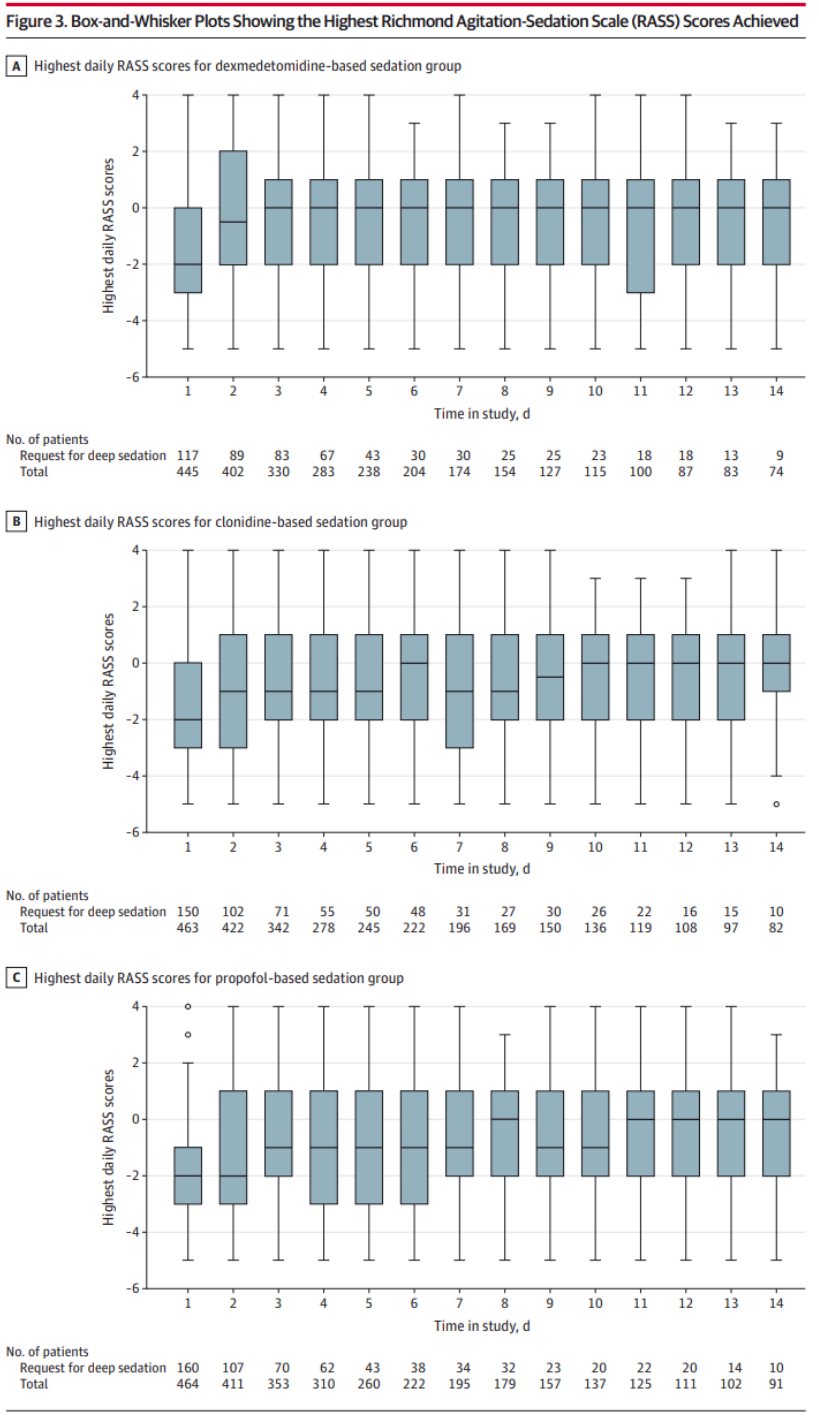
- High compliance with allocated treatment across groups
- Median duration of administration 4 days (all groups)
- High proportion of patients continued to receive some propofol in intervention groups

	Median daily dose (day 2-7)
Propofol Group	22-26 mg/kg/24 hours
Dexmedetomidine Group Dexmedetomidine infusion Propofol infusion	9-15 micrograms/kg/24 hours 4-7 mg/kg/24 hours
Clonidine Group Clonidine infusion Propofol infusion	15-22 micrograms/kg/24 hours 8-10 mg/kg/24 hours

Sedation status during intervention

Clinician request for deeper sedation typically:
20-25% days 2-4 across all groups
≈ 15% day 5 onwards

>75% of patients achieved the target RASS of ≥ -2 on most study days in all groups



Results – outcomes

Numbers included in analysis population

	N (%)
Total	1404
Allocated Treatment	
Dexmedetomidine	457 (33%)
Clonidine	476 (34%)
Standard Care	471 (34%)

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Primary Outcome – Time to Extubation

Modelling the cumulative incidence of successful extubation after taking into account the competing risk of mortality: *Fine and Gray proportional sub-distribution hazards regression analysis* (Fine and Gray, 1999)

Dexmedetomidine versus propofol comparison sHR (95% CI)	**Clonidine versus propofol comparison** sHR (95% CI)
1.09 (0.96 to 1.25) P = 0.20	1.05 (0.95 to 1.17) P = 0.34

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Hierarchy of analyses

No further testing as neither superiority comparison was statistically significant when compared against propofol.

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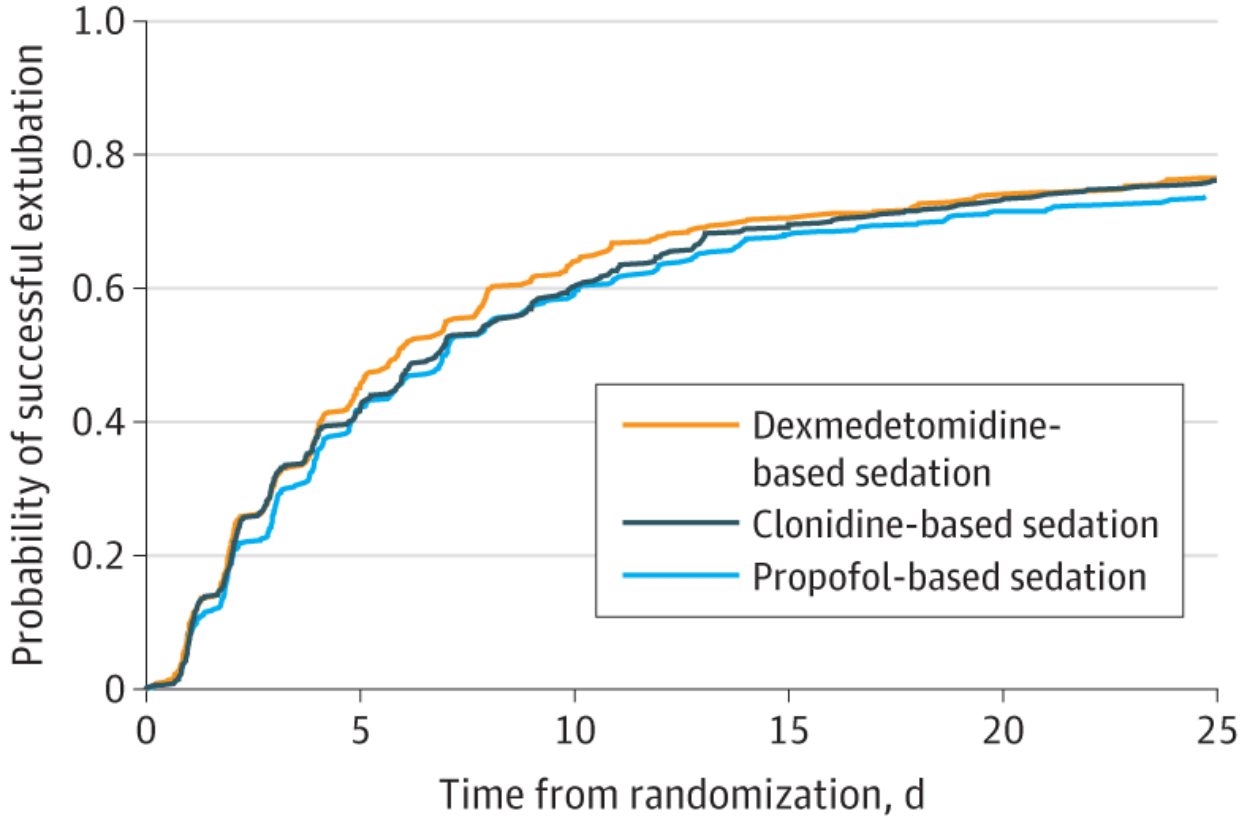
Cumulative incidence plot for Time to Extubation



No. at risk						
Dexmedetomidine-based sedation	456	325	234	175	129	104
Clonidine-based sedation	476	343	249	195	160	125
Propofol-based sedation	471	357	265	206	158	127

Walsh TS, et al. Dexmedetomidine- or Clonidine-Based Sedation Compared With Propofol in Critically Ill Patients: The A2B Randomized Clinical Trial. JAMA. 2025;334(1):32–45. doi:10.1001/jama.2025.7200

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Absolute difference measure: Difference in percentage of patients successfully extubated within 7 days

Dexmedetomidine versus propofol comparison Percentage difference (95% CI)	**Clonidine versus propofol comparison** Percentage difference (95% CI)
3.13% (-2.33% to 8.43%)	1.77% (-3.25% to 6.90%)

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Pre-defined sensitivity analysis: cause-specific hazard model given patient is alive

Cox frailty proportional hazards regression model, with censoring for deaths or loss to follow-up in ICU while on MV.

Dexmedetomidine versus propofol comparison HR (95% CI)	**Clonidine versus propofol comparison** HR (95% CI)
1.07 (0.93 to 1.24) P = 0.36	1.07 (0.93 to 1.24) P = 0.36

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Pre-defined analysis: Survival time to ICU mortality

Modelling the cause-specific hazard of death in ICU in patients who were still on MV. Cox frailty proportional hazards regression model, with censoring for extubation and loss to follow-up.

Dexmedetomidine versus propofol comparison sHR (95% CI)	**Clonidine versus propofol comparison** sHR (95% CI)
0.96 (0.71 to 1.30) P = 0.80	0.99 (0.72 to 1.34) P = 0.92

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Pre-defined analysis: Adherence population (N=1329)

Same statistical model as primary analysis but only including those patients receiving allocated treatment on the day of randomisation.

Dexmedetomidine versus propofol comparison sHR (95% CI)	**Clonidine versus propofol comparison** sHR (95% CI)
1.11 (0.97 to 1.28) P = 0.13	1.07 (0.96 to 1.20) P = 0.19

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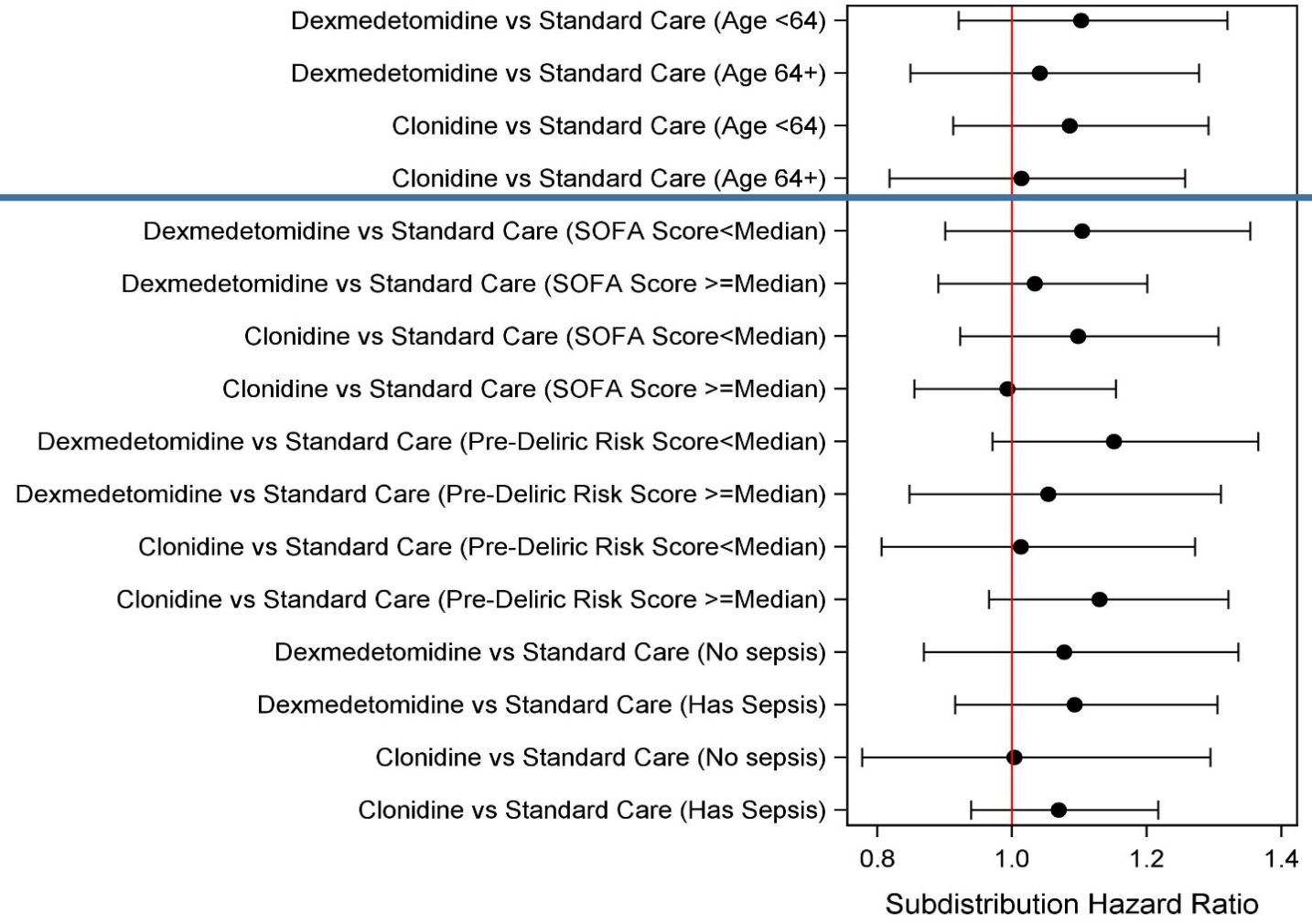
Pre-defined Sub-group analyses – primary outcome



P = 0.647

P = 0.684

P = 0.550

P = 0.416

P = 0.532

P = 0.504

P = 0.922

P = 0.694

Age as continuous variable (per year difference):
Age*dexmedetomidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)
Age*clonidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)

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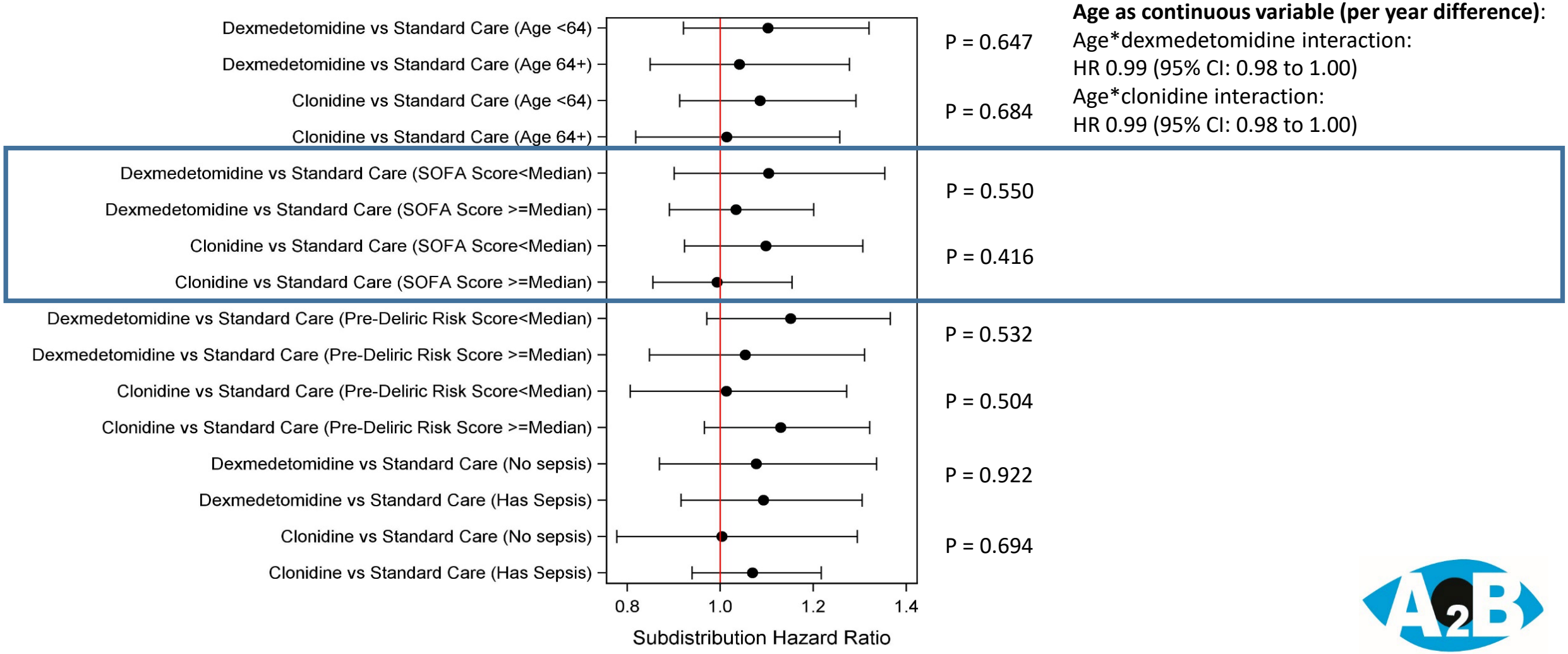
Pre-defined Sub-group analyses – primary outcome



Age as continuous variable (per year difference):
Age*dexmedetomidine interaction:
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Age*clonidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)

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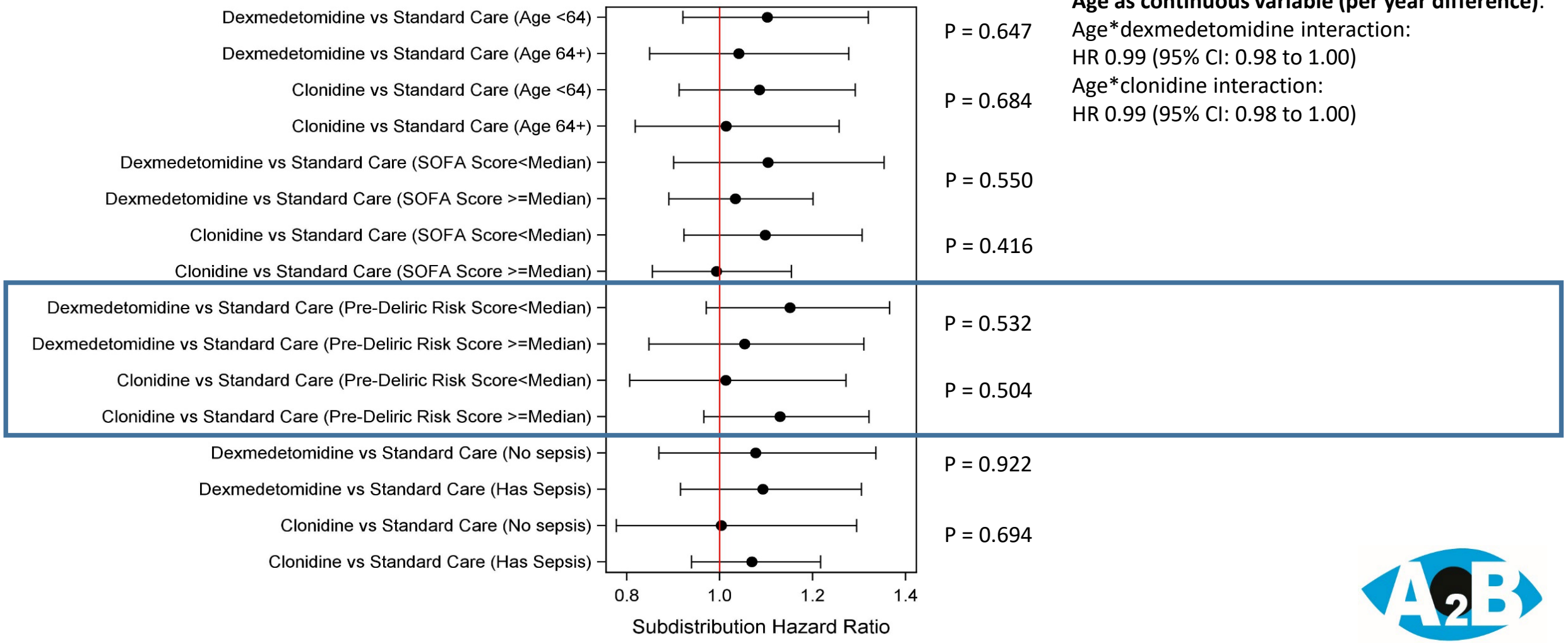
Pre-defined Sub-group analyses – primary outcome



Age as continuous variable (per year difference):
Age*dexmedetomidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)
Age*clonidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)

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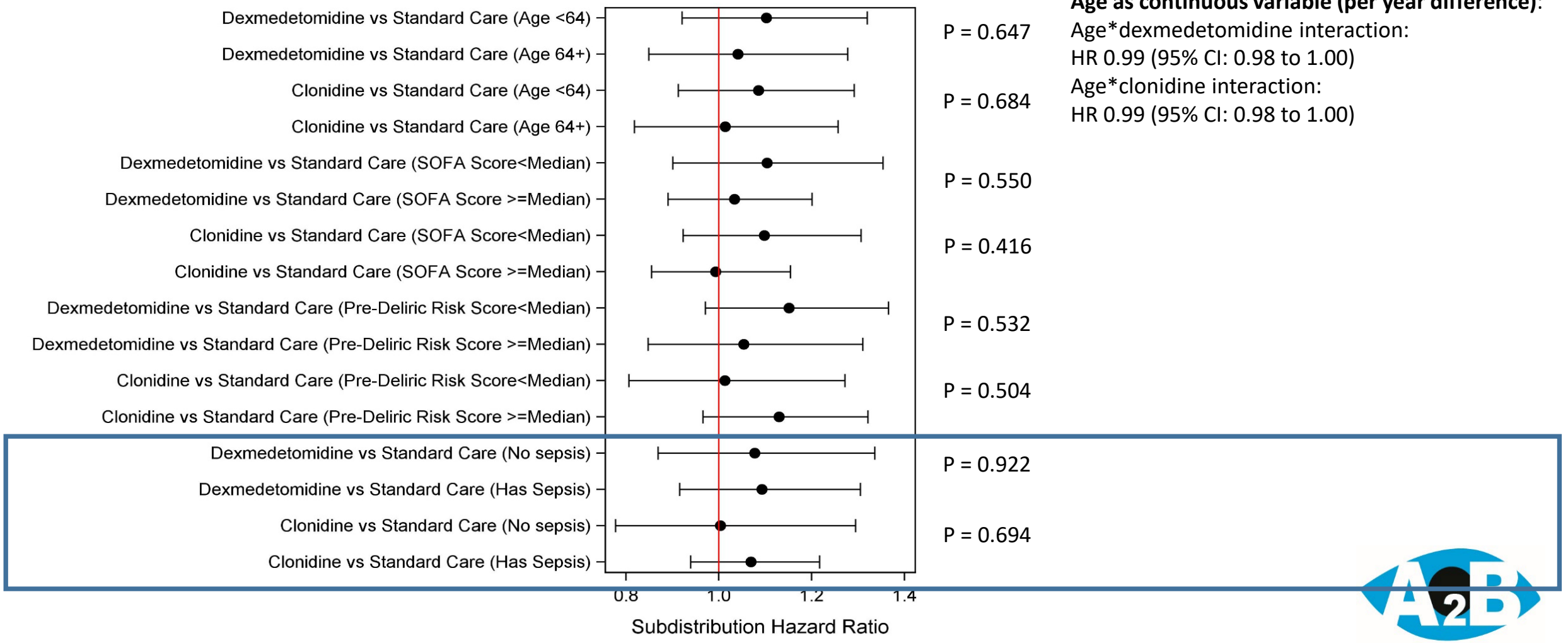
Pre-defined Sub-group analyses – primary outcome



Age as continuous variable (per year difference):
Age*dexmedetomidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)
Age*clonidine interaction:
HR 0.99 (95% CI: 0.98 to 1.00)

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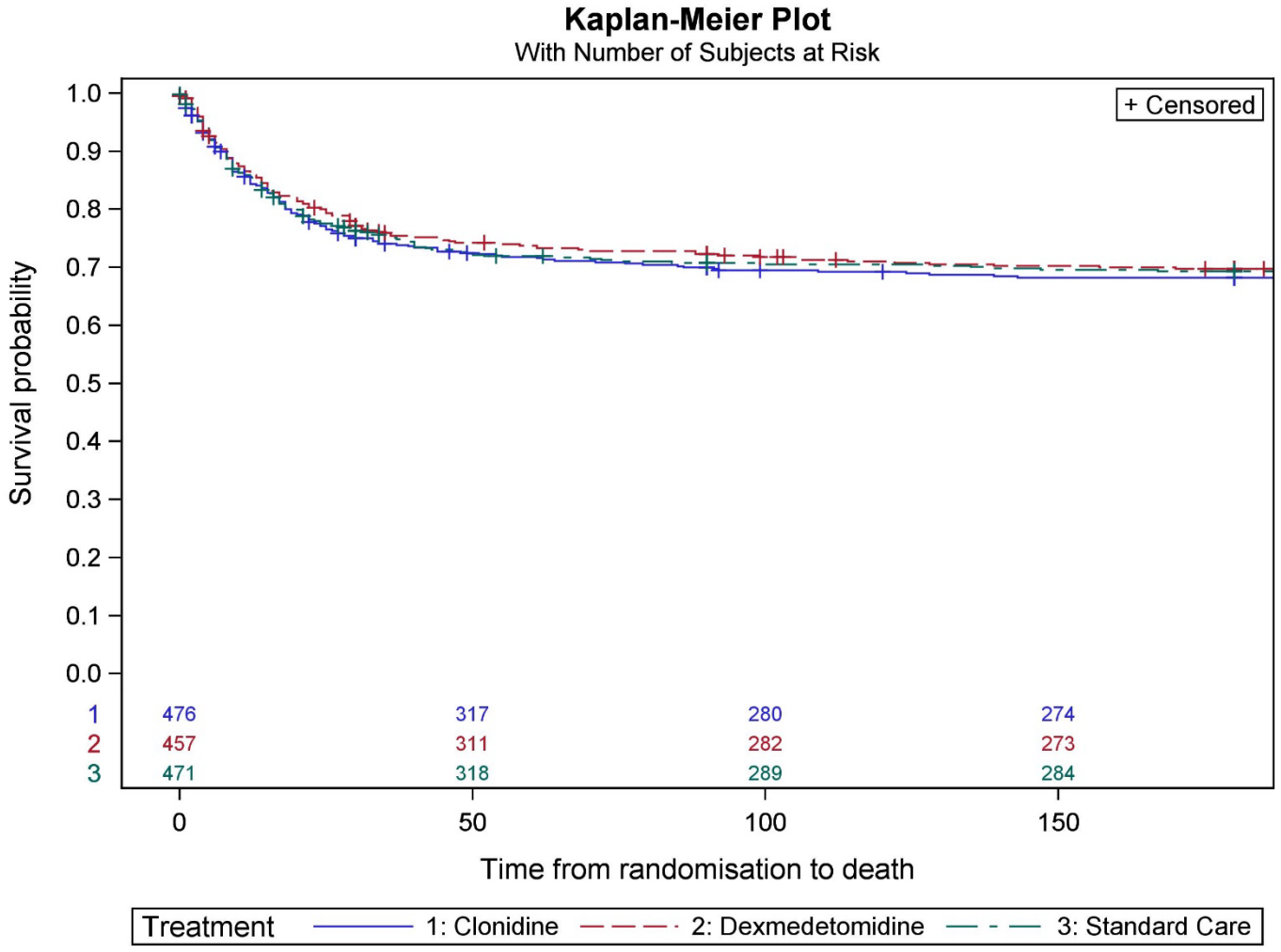
Secondary Outcomes – 90 days mortality



90 days mortality Number (%)		
Propofol (N = 471)	**Dexmedetomidine** (N = 457)	**Clonidine** (N = 476)
135 (29)	122 (27)	138 (29)

90 days mortality Hazard Ratio (95% CI)	
Dexmedetomidine vs propofol comparison	**Clonidine vs propofol comparison**
0.95 (0.74 to 1.21)	1.03 (0.82 to 1.31)

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Survival time to all-cause mortality anywhere (within 6 months of randomisation)

Cox frailty proportional hazards regression model, with censoring only for loss to follow-up/full withdrawals.

Dexmedetomidine versus propofol comparison HR (95% CI)	**Clonidine versus propofol comparison** HR (95% CI)
0.98 (0.77 to 1.24) P = 0.87	1.04 (0.82 to 1.31) P = 0.74

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Secondary Outcomes –Mortality interaction with age

Treatment comparison	Hazard Ratio (95%CI)
Dexmedetomidine versus Propofol (Age <64 years)	0.87 (0.61 to 1.25)
Dexmedetomidine versus Propofol (Age ≥64 years)	1.15 (0.84 to 1.58)
Clonidine versus Propofol (Age <64 years)	0.93 (0.65 to 1.34)
Clonidine versus Propofol (Age ≥64 years)	1.15 (0.84 to 1.56)

No interaction with age

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Secondary Outcomes – Time from randomisation to ICU Discharge

Dexmedetomidine versus propofol comparison HR (95% CI)	**Clonidine versus propofol comparison** HR (95% CI)
1.05 (0.92 to 1.19)	1.01 (0.91 to 1.12)

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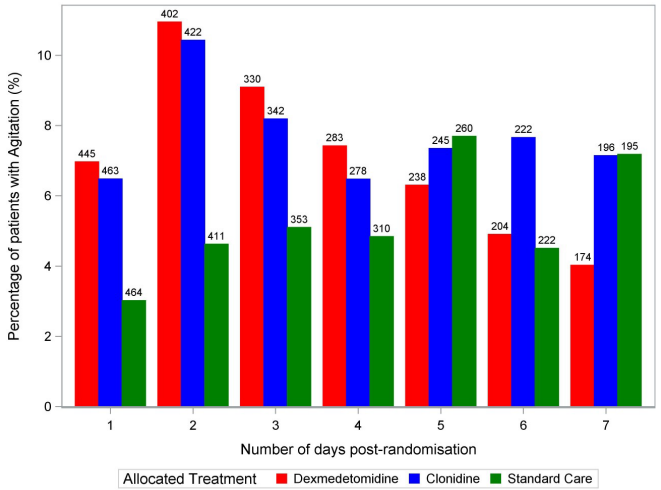
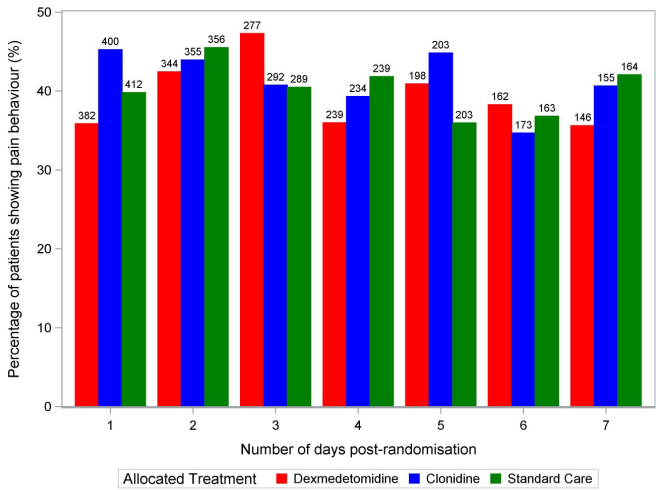
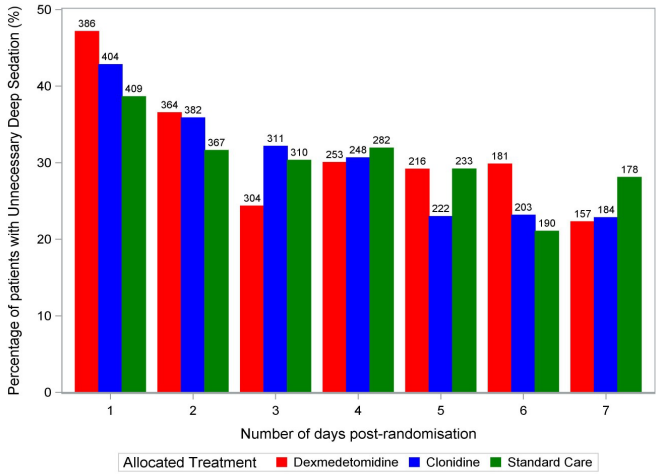
Secondary Outcomes – Sedation Quality

Agitation

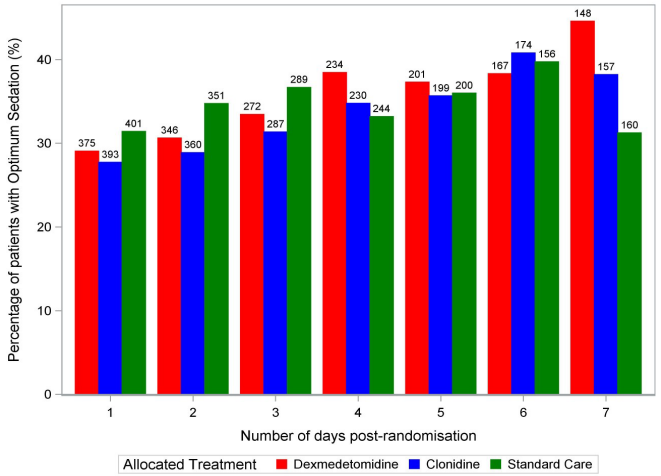


Pain behaviour





Unnecessary deep sedation



Overall optimum sedation

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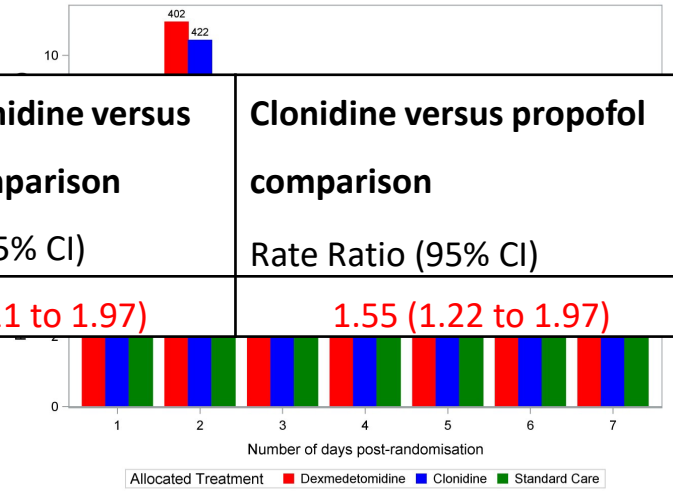
Secondary Outcomes – Sedation Quality

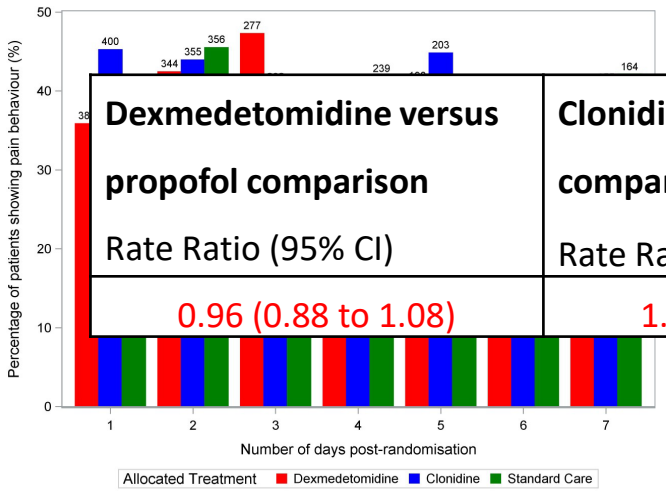
Agitation

Dexmedetomidine versus propofol comparison	Clonidine versus propofol comparison
Rate Ratio (95% CI)	Rate Ratio (95% CI)
1.54 (1.21 to 1.97)	1.55 (1.22 to 1.97)



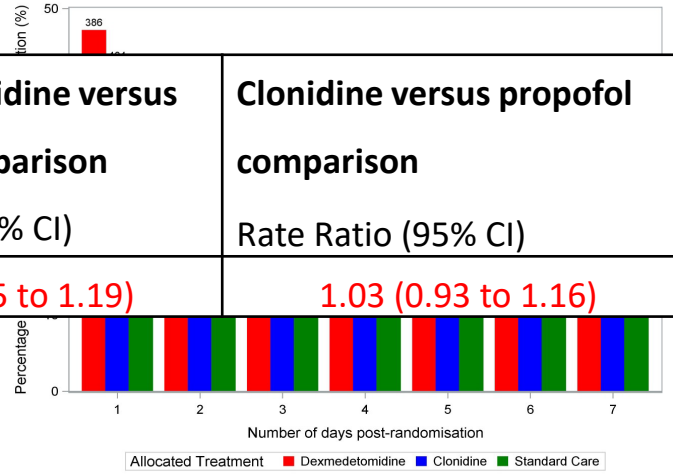
Pain behaviour

Dexmedetomidine versus propofol comparison	Clonidine versus propofol comparison
Rate Ratio (95% CI)	Rate Ratio (95% CI)
0.96 (0.88 to 1.08)	1.03 (0.93 to 1.14)



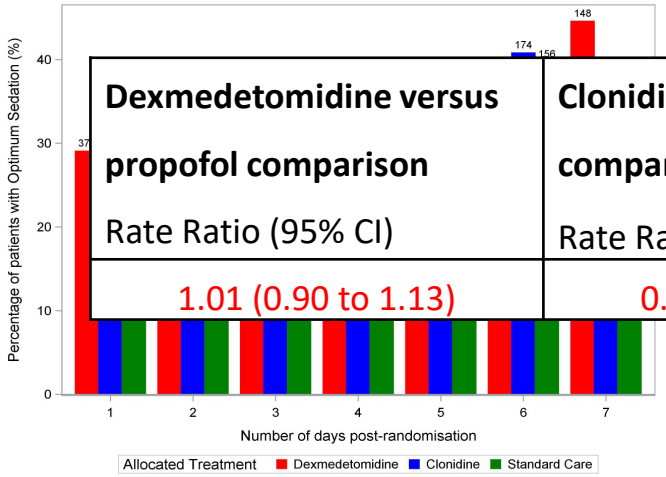
Unnecessary deep sedation

Dexmedetomidine versus propofol comparison	Clonidine versus propofol comparison
Rate Ratio (95% CI)	Rate Ratio (95% CI)
1.06 (0.95 to 1.19)	1.03 (0.93 to 1.16)



Overall optimum sedation

Dexmedetomidine versus propofol comparison	Clonidine versus propofol comparison
Rate Ratio (95% CI)	Rate Ratio (95% CI)
1.01 (0.90 to 1.13)	0.95 (0.85 to 1.06)



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Safety Outcomes – Cardiovascular Adverse events

Cardiovascular events on any days during intervention period	**Propofol (N = 471)**	**Dexmedetomidine (N = 457)**	**Clonidine (N = 476)**	**Dexmedetomidine versus propofol comparison** Rate ratio (95% CI)	**Clonidine versus propofol comparison** Rate ratio (95% CI)
Severe bradycardia Number (%) Rate of severe bradycardia during intervention period	93 (20%)	149 (33%)	152 (33%)	1.62 (1.36 to 1.93)	1.58 (1.33 to 1.88)
Cardiac arrythmia Number (%) Rate of cardiac arrythmia during intervention period	170 (36%)	167 (37%)	171 (37%)	1.27 (1.15 to 1.40)	1.04 (0.94 to 1.16)
Cardiac arrest Number (%) Rate of cardiac arrest during intervention period	25 (5%)	25 (6%)	24 (5%)	1.23 (0.75 to 2.04)	0.94 (0.55 to 1.60)

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Process outcome – key findings

- 69 interviews with clinical and research staff early and late in the trial
- Multiple factors influence sedation practice within trial context:
  - Context-specific sedation ‘culture’
  - Clinician preference and equipoise
  - Staff capacity, training, capability
  - Safety concerns
  - ‘Engrained’ practices (eg. overnight deeper sedation)

Process outcome – clinical staff views of alpha2-agonists

- Confidence and experience using drugs
  - Nurse experience and support
  - Impact of COVID19 on staff
- Hesitancy up-titrating dosing
  - Concerns about bradycardia and hypotension
  - Concerns about use in younger patients
- Hesitancy titrating to ‘light’ sedation
  - Fear of agitation
  - Safety-related adverse events, eg accidental extubation
  - Culture of overnight deeper sedation
- Desire to keep propofol as ‘familiar safety net’

Summary

- Neither dexmedetomidine nor clonidine were significantly better than propofol regarding time to successful extubation

- There was a higher rate of agitation in the dexmedetomidine and clonidine groups.
- There was a higher rate of severe bradycardia in the dexmedetomidine and clonidine groups.

- Process evaluation indicated factors related to clinician views, confidence, and concerns about safety that influenced ‘real world’ implementation of the interventions

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Thank you