Case Study: Approval of Dexmedetomidine for ICU Sedation

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Potential Conflict of Interest

- Co-patent holder of DEX for sedation in 1987
- Stanford re-assigned its IP to Farmos (who synthesized the molecule)
- Stanford Received $50K/year X 5 years
- Stanford passed on funds to Maze Lab
- Abbott/Hospira provided MM with
  - Consulting contract to assist in protocol development for Phase 3
  - Research Grant to investigate Mechanism of Action
  - No support for last 10 years
  - No Royalties on sales of DEX

Background

- 870 published RCTs addressing the use of Dexmedetomidine (DEX)
  - Patient Populations
    - Pediatric and Adult
  - Indications from
    - Procedural Sedation
    - Drug and Alcohol Withdrawal
  - Different Settings
    - Ambulatory
    - Critical Care
  - Different Routes of Administration
    - Parenteral, Oral, Nasal, Buccal, Epidural, Caudal, Nerve Block
- How did it all begin
  - Once upon a time……

What is the Indication for a Pleiotropic Drug?

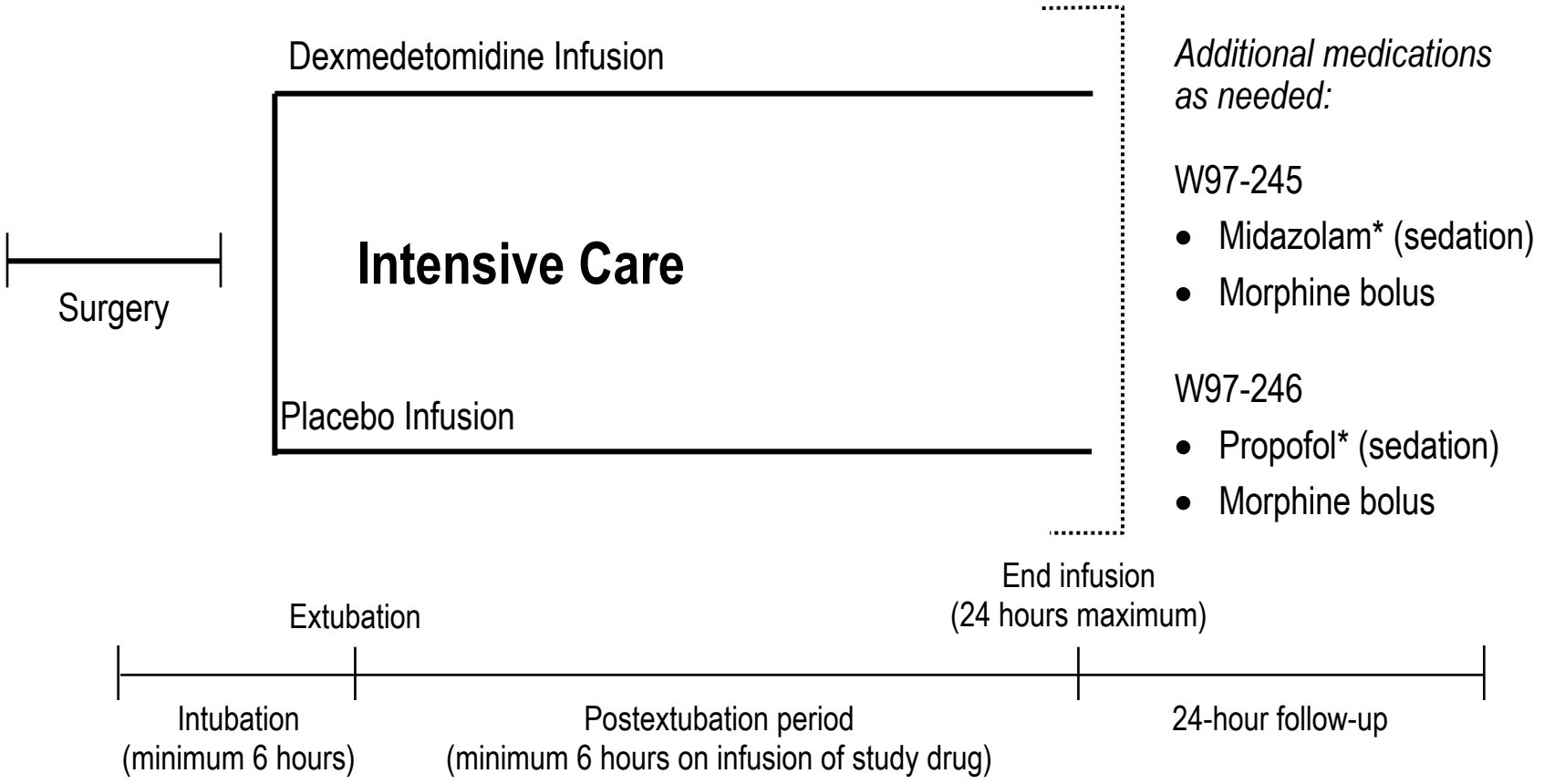
- α_2 adrenergic receptors ubiquitously distributed on almost all cell types
- Produce wide range of pharmacologic effects
  - Sedation/anesthesia
  - Analgesia
  - Sympatholysis
  - Anxiolysis
  - Anti-shivering
  - Anti-inflammatory
- Dr. Romeo Bachand (consultant for Abbott) hosted SAB meeting in 1997
  - ICU Sedation *vs* Premedication
- Pre-IND Meeting with FDA
  - Accepted DEX for ICU Sedation with Placebo control
  - No comparator study needed
- Enrollment into Phase 3 RCT Completed in 12-week period in summer 1998

Trial Design and Objectives

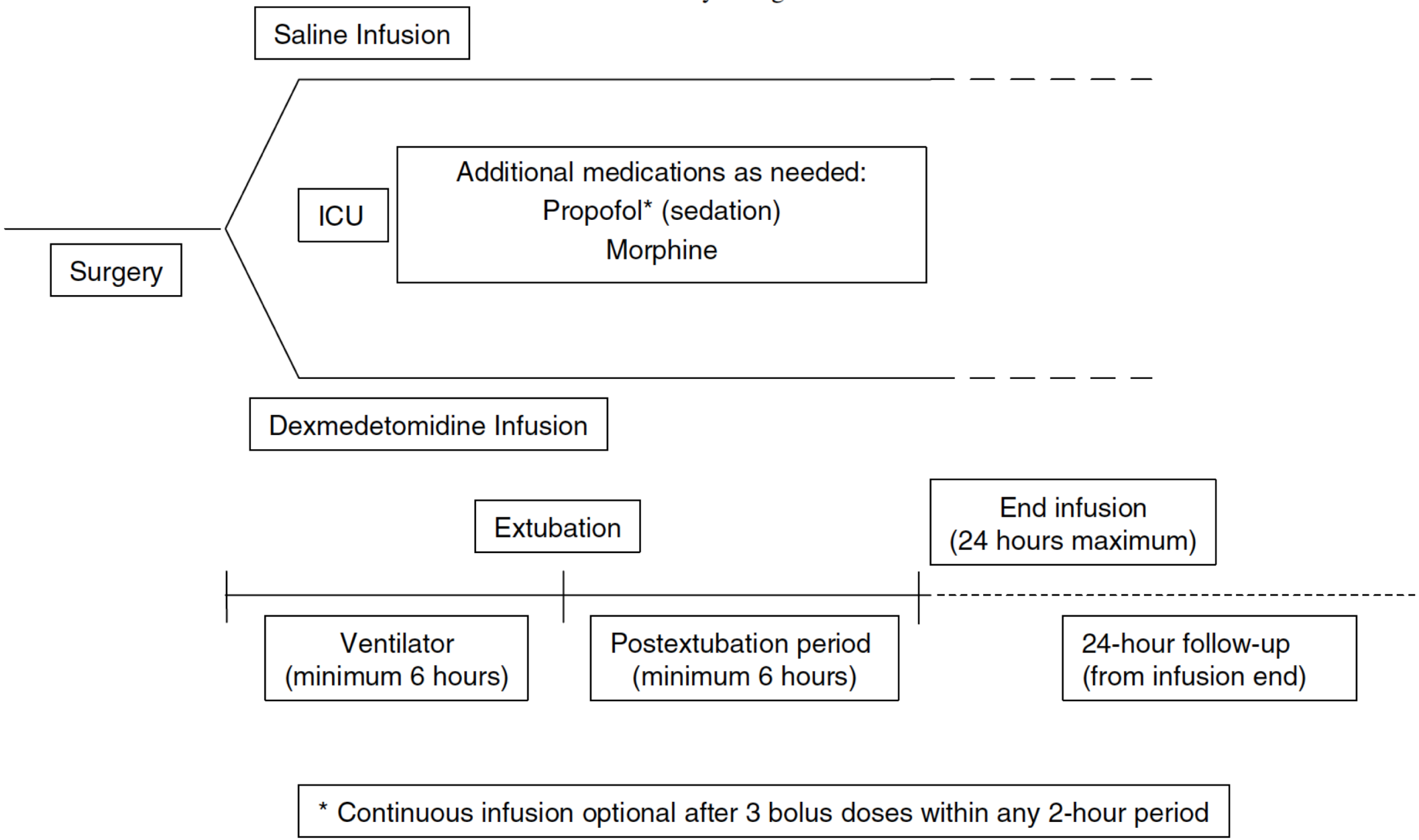
- Per the FDA, two pivotal placebo-controlled RCTs for registration
  - W97-245 – midazolam for rescue sedation
  - W97-246 – propofol for rescue sedation
- Primary Objective

  To evaluate whether there is a difference in rescue sedative use to achieve a prescribed level of sedation in mechanically-ventilated postoperative subjects randomized to either dexmedetomidine (DEX) or placebo (saline).
- Secondary Objective
  - To evaluate the safety and tolerability of study drugs in postoperative mechanically-ventilated subjects.
  - To evaluate whether there is a difference in rescue morphine use to achieve adequate pain control in mechanically-ventilated postoperative subjects
  - To evaluate whether there is a difference in duration of weaning, and time to extubation in subjects receiving DEX *vs* placebo
  - Nurses Assessment during mechanical ventilation of
    - Tolerance of the endotracheal tube/ventilator
    - Ease of Communication
    - Ease of Management
  - Patient Recall of their ICU experience

Phase III Study Design



Study Design



Patients and Methods

- Elective Surgery
  - Requiring a minimum of 6h postop mechanical ventilation
  - ICU stay to include no less than 6h post-extubation for study drug infusion
  - All surgeries except intracranial
- Exclusion Criteria
  - CNS Trauma; Use of NMBs, epidural or spinal anesthesia; gross obesity; allergy; uncontrolled DM
- Initiate Study Drug within 1 h of ICU admission
  - to allow study drug effect prior to
    - patient's awakening
    - requirement for any other sedative or analgesic medication
  - If sedative needed prior to administration of study drug
    - Midazolam 0.1mg/kg
    - Propofol 0.2 mg/kg
- Assessments while receiving study drug infusion (24h max infusion period)
  - 6h mechanical ventilation
  - 6h post-extubation
- Assessments for 24h after termination of study drug infusion

Titration of Sedative Infusion

- Target Ramsay sedation score
  - 3 or higher during intubation
  - 2 or higher post-extubation
- 10-minute loading infusion
  - 1.0 mcg/kg of dexmedetomidine or placebo
- Initial maintenance infusion of 0.4 mcg/kg/h
  - the rate could be adjusted in increments of 0.1 mcg/kg/h
- Subsequent maintenance infusion
  - maintained in the range of 0.2 to 0.7 mcg/kg/h
- Supplemental Sedation
  - Midazolam up to 3 X 0.02 mg/kg boluses in 1st h; thereafter infusion 0.01-0.02 $mg.kg^{-1}.h^{-1}$
  - Propofol up to 3 X 0.2 mg/kg boluses in 1st h; thereafter infusion 0.5-4 $mg.kg^{-1}.h^{-1}$
- Supplemental Analgesia
  - 2mg boluses of morphine in response to patient communication or autonomic signs

Statistical Analysis for ITT subjects

- 150 patient/group to provide
  - 80% power, to detect a statistical difference ($p = <0.05$; 2-tailed) in supplemental sedation required between DEX and placebo (saline) groups
  - If ≥ 90% of enrolled patients were evaluable
- Effect Size of 0.35 in 24 h use of supplemental sedatives in DEX
  - From an expected propofol 70 mg/kg in placebo to 20mg/kg in DEX group (± 65% reduction)
- Analysis of variance (ANOVA) modeled for interactions
  - Treatment
  - Center
  - treatment-by-center
- Chi square for proportion of patients in each supplemental category
- Kaplan-Meier Survival Curves with log-rank analysis
  - Weaning duration
  - Time to Extubation (up to a maximum of 24h)
- Total Dose of morphine administered during study drug administration
- Treatment-emergent adverse events

Results of W97-246

- 72% of the study population were male
- CABG surgery most common (~ 50%)
- Mean Age 61.2 for DEX and 63 for placebo
- Ramsay Scores achieved: DEX = 3.4; Placebo = 3.1
- During Mechanical Ventilation
  - DEX required 71.6 ±17.5 mg vs placebo of 513.2±55.6 mg propofol (p=0.0001)
- Total Dose during study drug administration
  - DEX required 5.3±1.24 mg/hr and placebo 39.1±4.13 mg/hr (p<0.0001)
- Morphine use
  - Dex required 0.4 ± 0.04 mg/h and placebo 0.9 ± 0.05 mg/h (p<0.0001)

Amount of Supplemental Propofol for RSS of >2 during Mechanical Ventilation and RSS >1 post-Extubation

	Dexmedetomidine	Control	*P* Value
During assisted ventilation			
n	203	198	
Total dose (mg)	71.6 ± 17.51	513.2 ± 55.6	< .001
n[a]	198	195	
Mean rate (mg/h)	8.6 ± 1.9	65.6 ± 6.8	< .001
During study drug administration			
n	203	198	
Total dose (mg)	80.0 ± 21.3	559.8 ± 60.5	< .001
Mean rate (mg/h)	5.3 ± 1.2	39.1 ± 4.1	< .001

Values are expressed as mean total dose ± SEM. The *P* values are from an analysis of variance.
a. Exact time of extubation missing for 5 dexmedetomidine patients and 3 control patients.

Nursing Assessment & Patient Management Index

	Dexmedetomidine		Control	
	n	Score	n	Score
Overall sedation and tolerance of the intensive care unit[a]	180	1.5 ± 0.04	176	1.9 ± 0.06
Tolerance of endotracheal tube/ventilator[b]	180	1.3 ± 0.03	175	1.5 ± 0.04
Ease of communication with patient[c]	179	2.1 ± 0.07	176	2.4 ± 0.08
Ease of management of the patient[b]	178	1.2 ± 0.03	175	1.6 ± 0.05
Patient Management Index[d]	177	6.1 ± 0.12	174	7.3 ± 0.18

a. 1 = *very easy*, 2 = *easy*, 3 = *moderate*, 4 = *difficult*.
b. 1 = *good*, 2 = *moderate*, 3 = *poor*.
c. 1 = *very easy*, 2 = *easy*, 3 = *moderate*, 4 = *difficult*, 5 = *not possible*.
d. The *P* value from the Cochran-Mantel-Haenszel row mean score statistic adjusted for center differences was < .001.

Mechanical Ventilation Requirements

Time (min) to Weaning (Mean ± SD)

- DEX - 30.4 ± 12.3
- Control - 63.1 ± 14.5

Time (min) to Extubation (Mean ± SD)

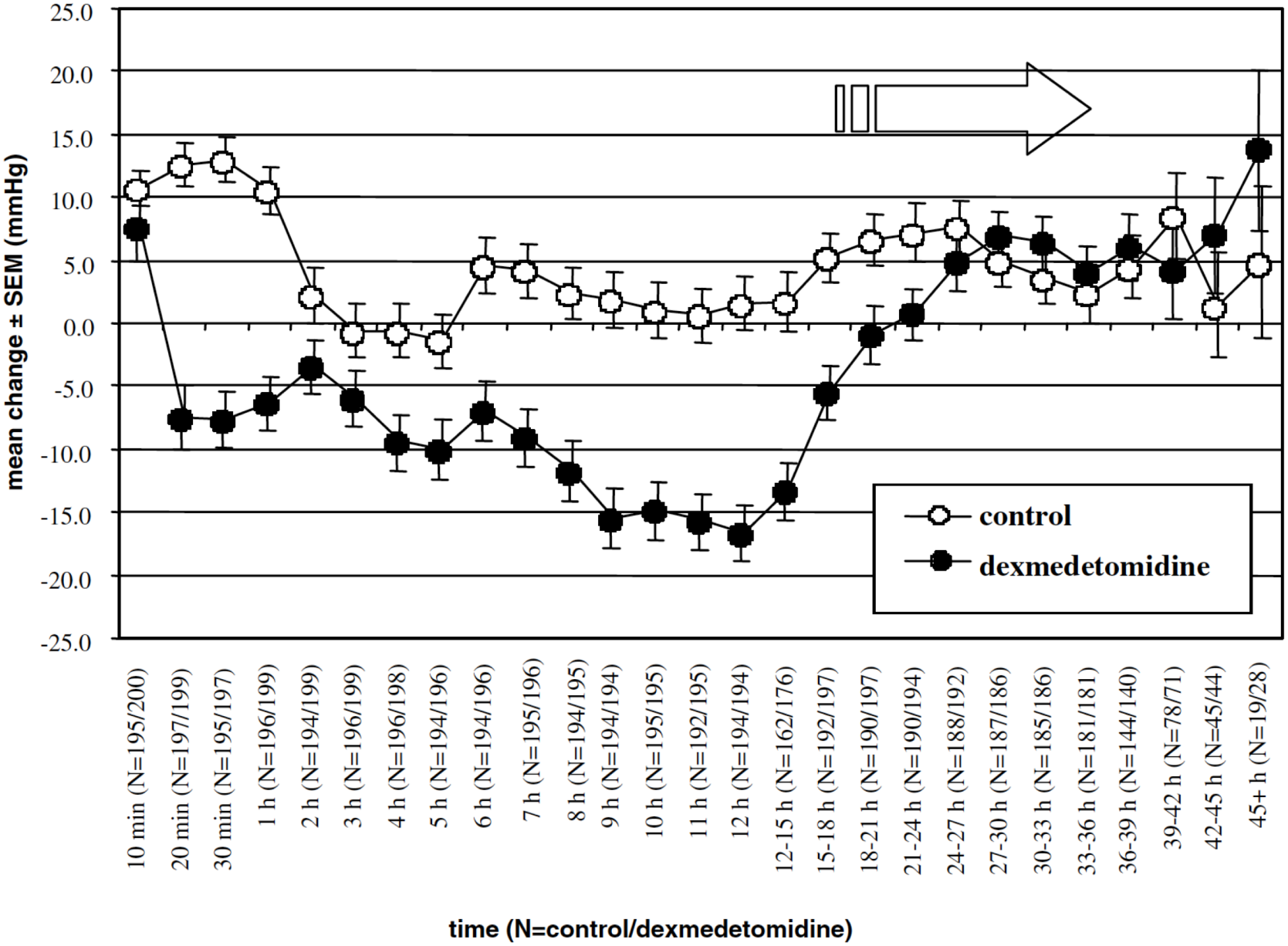
- DEX - 471.5 ± 15.9
- Control - 498.1 ± 43.9

Treatment-emergent Adverse Events

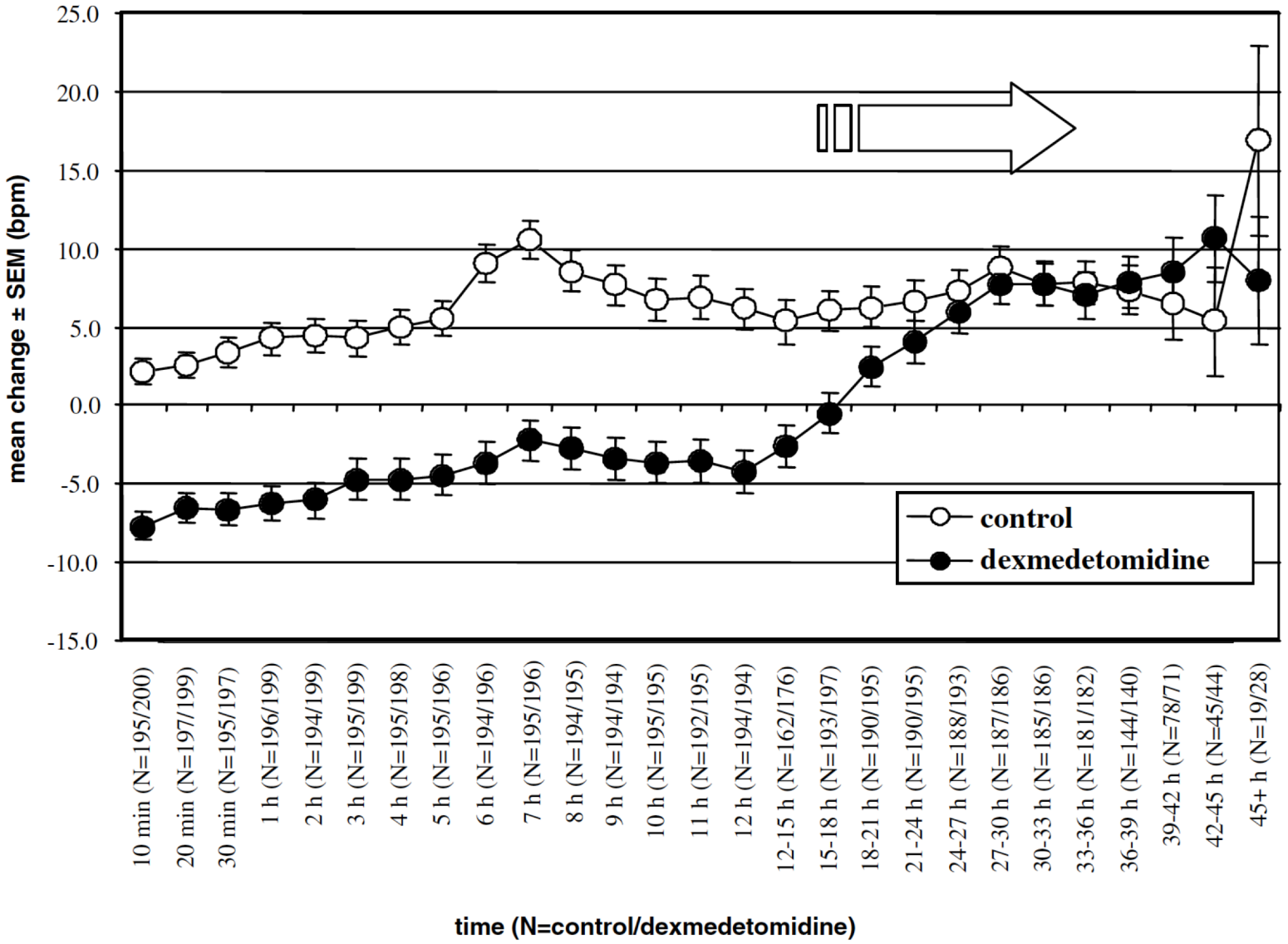
All Treated Patients	Dexmedetomidine (n = 203)	Control (n = 198)	*P* Value
Patients with at least 1 treatment-emergent adverse event	121 (60%)	112 (57%)	.545
Hypotension	61 (30%)	20 (10%)	< .001
Hypertension	24 (12%)	45 (23%)	.005
Nausea	22 (11%)	19 (10%)	.743
Bradycardia	18 (9%)	4 (2%)	.003
Vomiting	10 (5%)	11 (6%)	.826
Hypoxia	8 (4%)	5 (3%)	.575
Mouth dry	7 (3%)	1 (< 1%)	.068
Fever	6 (3%)	7 (4%)	.785
Tachycardia	4 (2%)	6 (3%)	.539
Hemorrhage	3 (1%)	7 (4%)	.216
Atrial fibrillation	3 (1%)	5 (3%)	.499
Acidosis	3 (1%)	5 (3%)	.499
Confusion	3 (1%)	6 (3%)	.333
Agitation	2 (< 1%)	6 (3%)	.171
Atelectasis	1 (< 1%)	9 (5%)	.010
Rigors	1 (< 1%)	8 (4%)	.019

Adverse events experienced by ≥ 3% of patients in either group. *P* values were calculated by Fisher's Exact Test. Terms are from the World Health Organization-Adverse Reaction Terms.

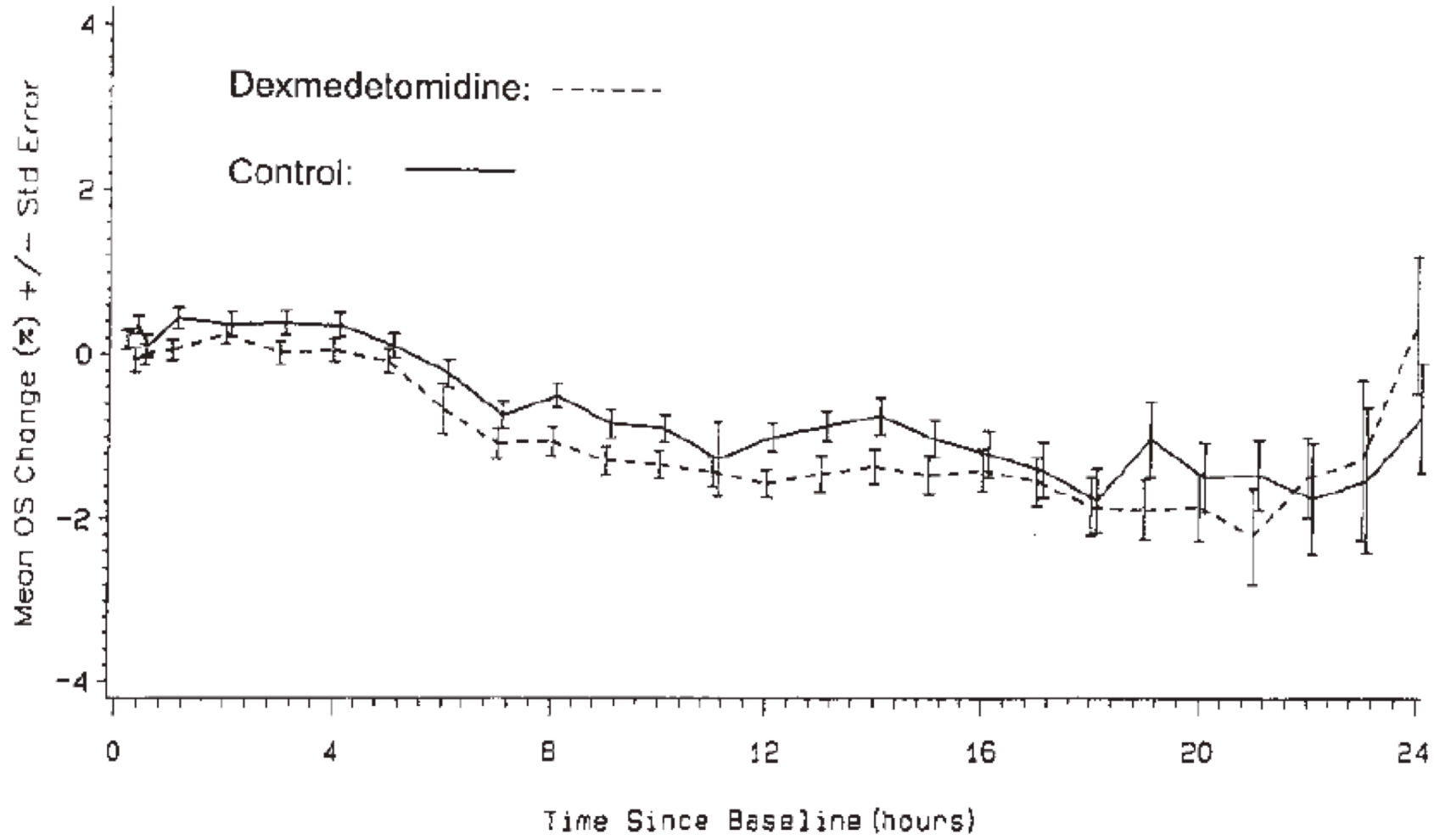
Change in Mean Systolic BP over 48h Study Period



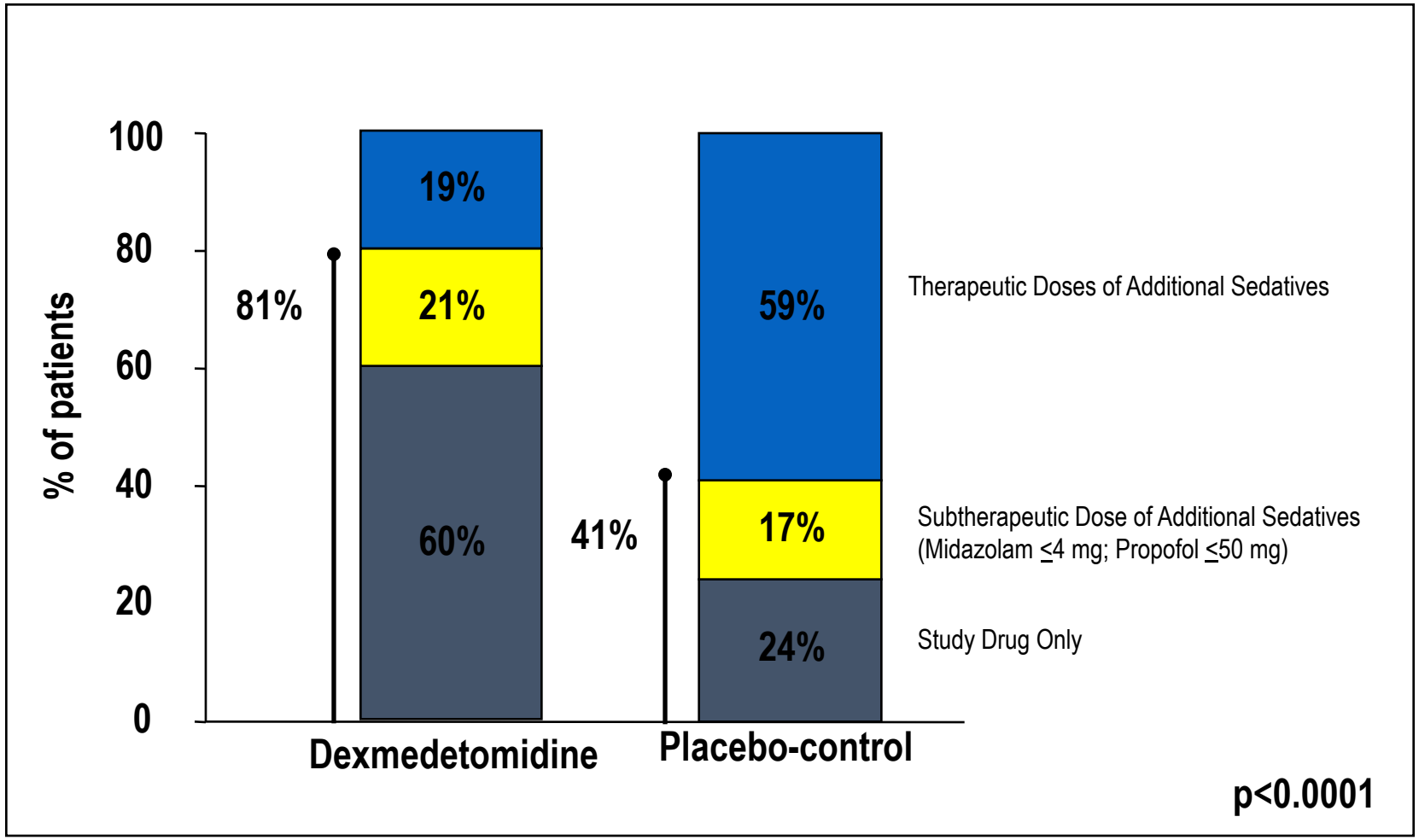
Mean change in heart rate over 48h Study Period



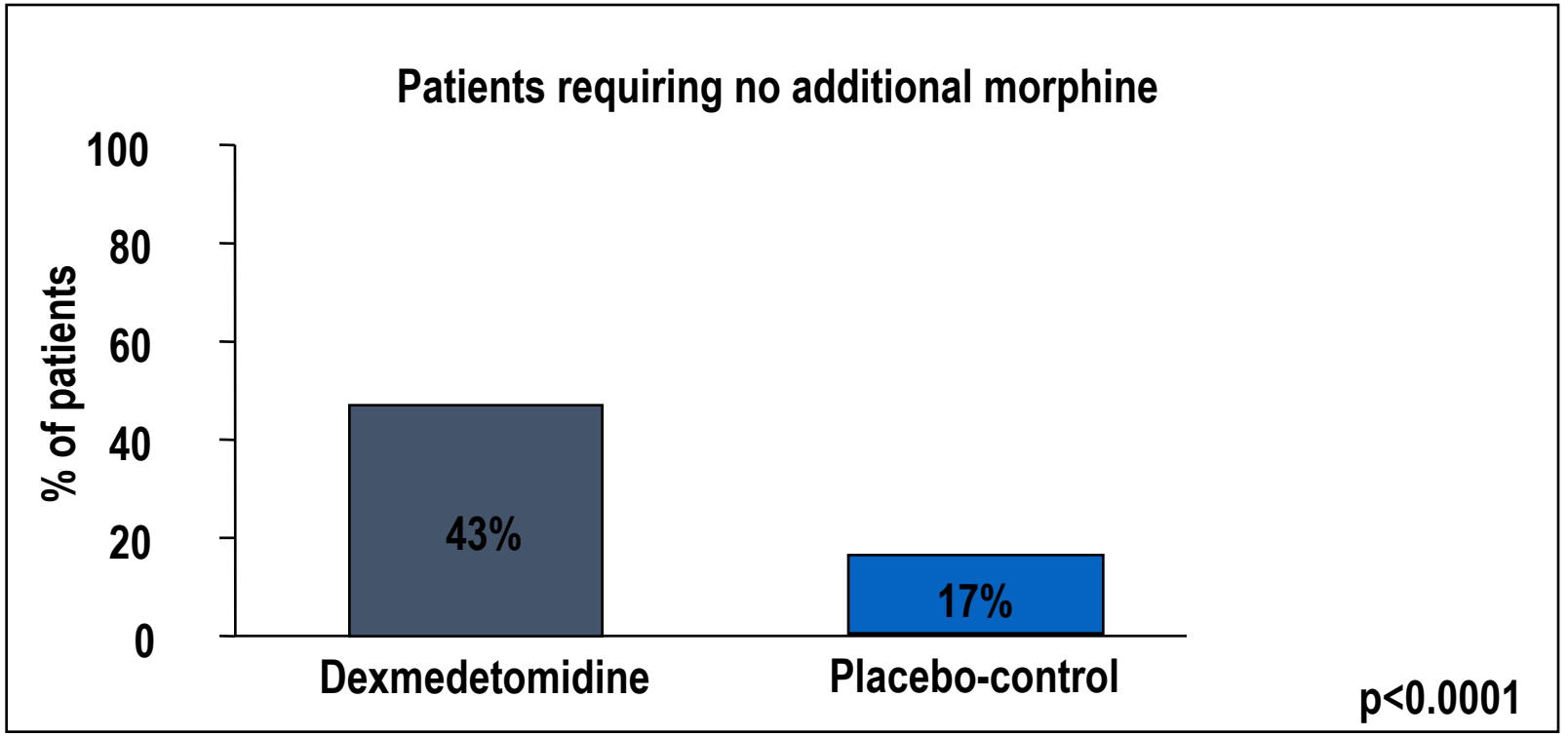
Percent Change in Oxygen Saturation During Study Drug Administration



Percentage of Patients that received therapeutic, subtherapeutic, or no supplemental midazolam

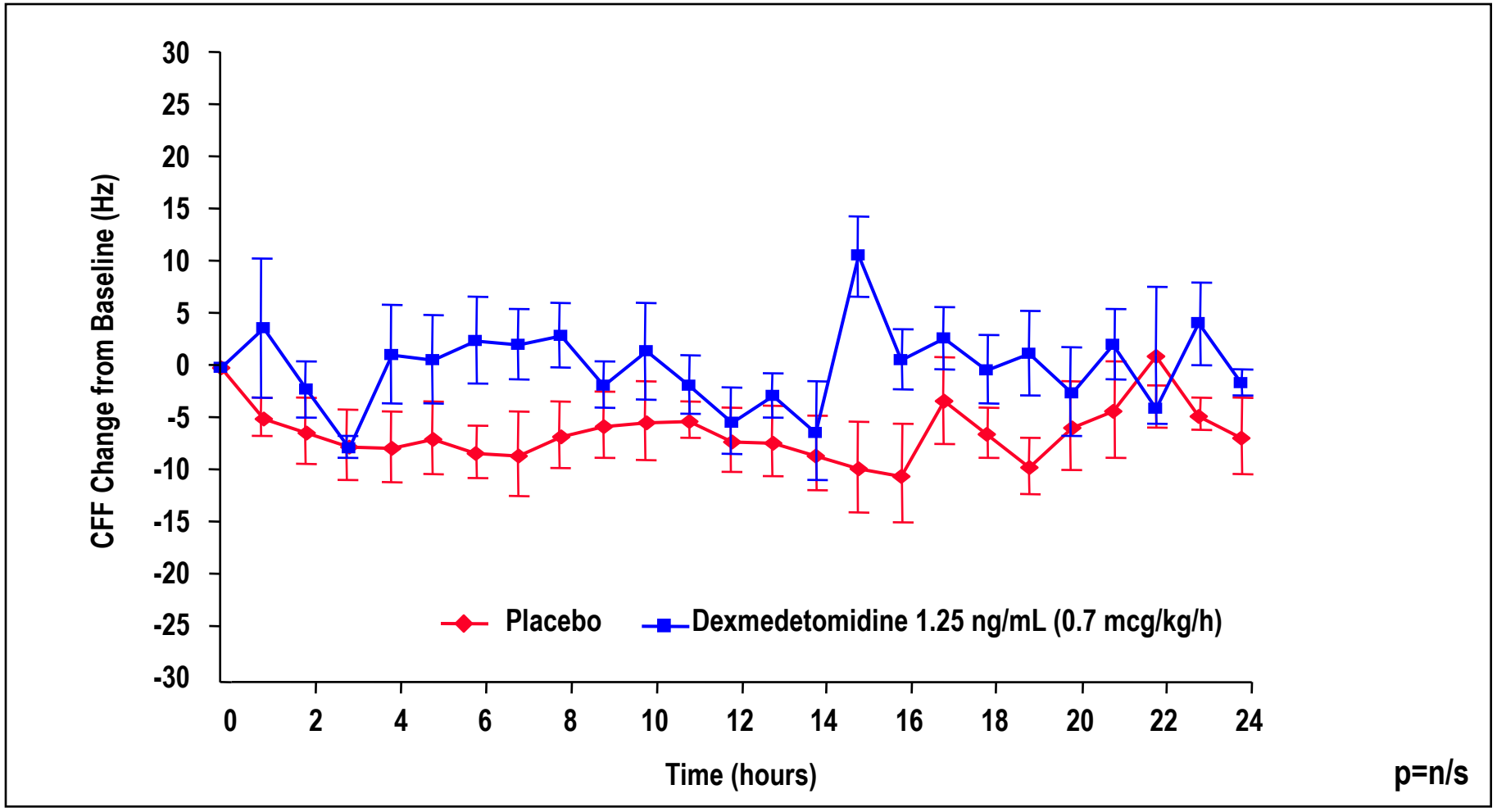


Percent of Patients requiring no Morphine



- **Total dose of morphine required by dexmedetomidine-treated patients was 6.2mg versus 12.5mg for the placebo-control group**

Rousability: CFF Change from Baseline



Results of Trial led to approval of the NDA in Feb 1999

Tom Willer of HPD Regulatory spoke with David Morgan at the FDA this afternoon regarding acceptance of the NDA. Per David Morgan, there are "no
outstanding issues with the submission."
Joan

ACHIEVING GOAL-DIRECTED SEDATION IN THE MEDICAL ICU: A COMPARISON OF DEXMEDETOMIDINE VERSUS A STANDARD SEDATIVE STRATEGY

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Vanderbilt University School of Medicine

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Contrary View by European Medicines Agency

- The claimed indication for dexmedetomidine of primary therapy (main and first line treatment) for sedation with analgesic properties in post surgical patients requiring intensive care is not supported by clinical data
- As far as sparing effect is concerned, what is the clinical relevance of that effect and what is the benefit in terms of clinical outcomes?
- In the absence of direct comparison to reference therapy, the benefit/risk assessment of the drug cannot be reliably assessed.
- Cardiovascular effects of dexmedetomidine raise a safety concern. Furthermore, patients at risk of serious cardiovascular events such as: cardiac arrest, cardiac failure, or myocardial infarction were not clearly defined as from the available data, the causal effect of dexmedetomidine cannot be completely excluded.

Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation: Two Randomized Controlled Trials JAMA. 2012;307(11):1151-1160

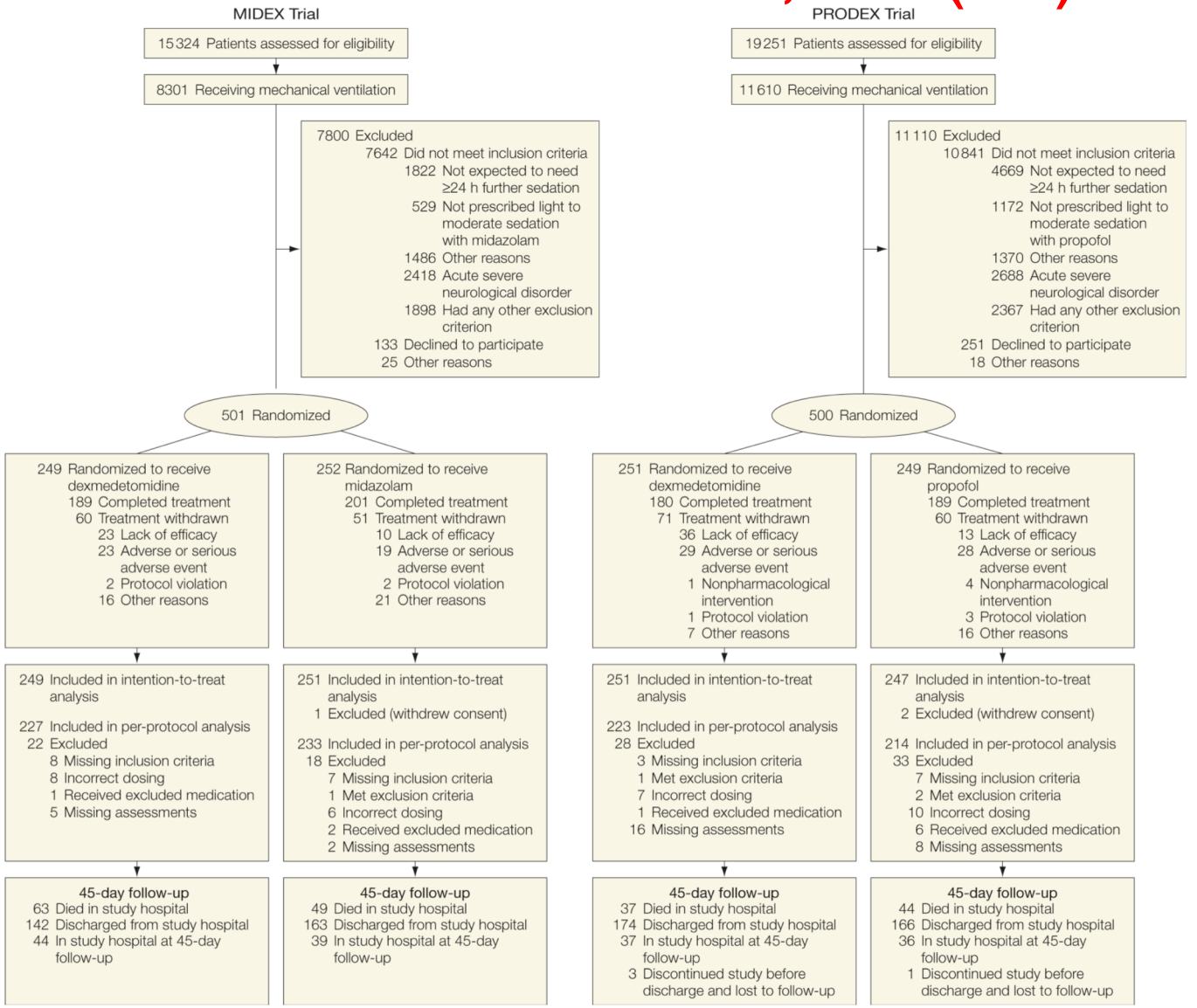


Table 1. Demographics, Diagnostic Groups, and Severity of Organ Failures at Baseline

	Dexmedetomidine vs Midazolam Study (MIDEX)			Dexmedetomidine vs Propofol Study (PRODEX)		
	Dexmedetomidine (n = 249)	Midazolam (n = 251)	*P* Value[c]	Dexmedetomidine (n = 251)	Propofol (n = 247)	*P* Value[c]
Male, No. (%)	153 (61.4)	175 (69.7)	.06	160 (63.7)	166 (67.2)	.45
Age, median (IQR), y	65 (55-74)	65 (55-74)	.98	65 (51-75)	65 (51-74)	.93
SAPS II, median (IQR)[a]	46 (36-56)	45 (34-56)	.53	48.0 (36-55)	44.5 (35-55)	.37
Main reason for admission to ICU, No. (%)						
Medical	182 (73.1)	171 (68.1)	.19	137 (54.6)	143 (57.9)	.38
Surgical	55 (22.1)	58 (23.1)		92 (36.7)	77 (31.2)	
Trauma	12 (4.8)	22 (8.8)		22 (8.8)	27 (10.9)	
Any infection at ICU admission, No. (%)	145 (58.2)	124 (49.4)	.049	136 (54.2)	127 (51.4)	.59
Organ failures (SOFA score >2), No. (%)						
Respiratory	149 (59.8)	154 (61.4)	.78	165 (65.7)	156 (63.2)	.58
Cardiovascular	152 (61.0)	151 (60.2)	.86	156 (62.2)	161 (65.2)	.52
Renal	37 (14.9)	42 (16.7)	.62	24 (9.6)	23 (9.3)	>.99
Coagulation	19 (7.6)	19 (7.6)	>.99	11 (4.4)	18 (7.3)	.18
Liver	2 (0.8)	3 (1.2)	>.99	1 (0.4)	1 (0.4)	>.99
Total SOFA score, median (IQR)[b]	7.0 (5.0-9.0)	7.0 (4.0-9.0)	.89	7.0 (5.5-9.0)	7.0 (5.0-9.0)	.88

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

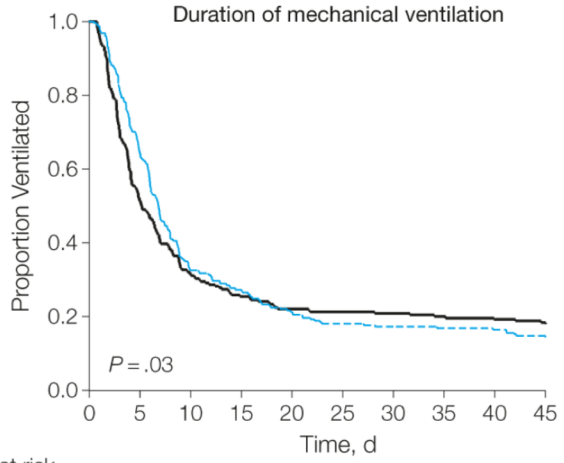
[a] The SAPS II range of possible values is 0-163; higher values indicate greater illness. The score was collected only after the protocol's first amendment requested it; the numbers of patients for each of the groups were 189, 186, 215, and 222, respectively.

[b] Sum of the SOFA scores excluding the central nervous system score (range of possible values: 0-20; higher scores indicate greater illness).

[c] For categorical variables, analyses used the Fisher exact test, and for continuous variables, analysis of variance.

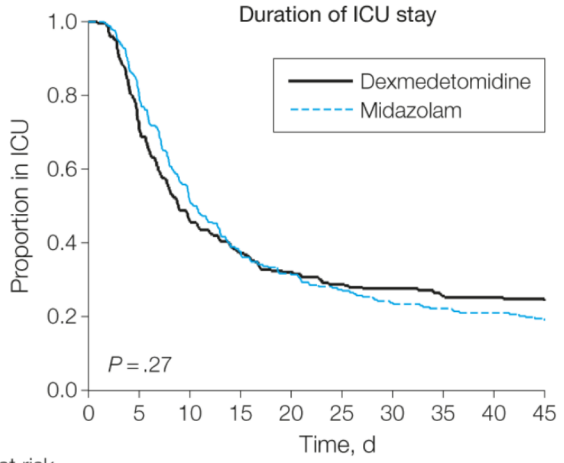
Duration of Mechanical Ventilation and ICU LoS

A MIDEX trial



No. of patients at risk

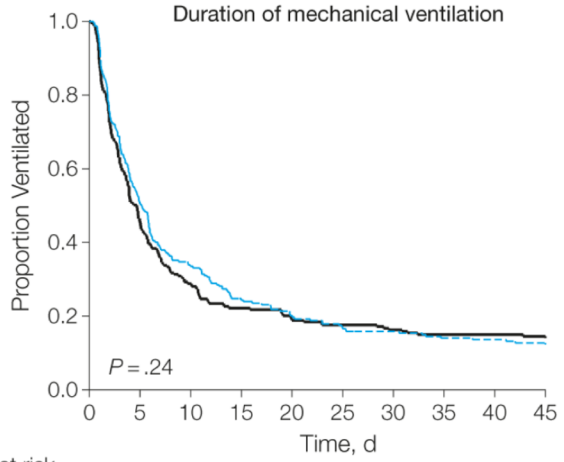
Dexmedetomidine	249	128	77	62	54	52	51	49	47	43
Midazolam	251	162	81	68	53	45	43	41	40	34



No. of patients at risk

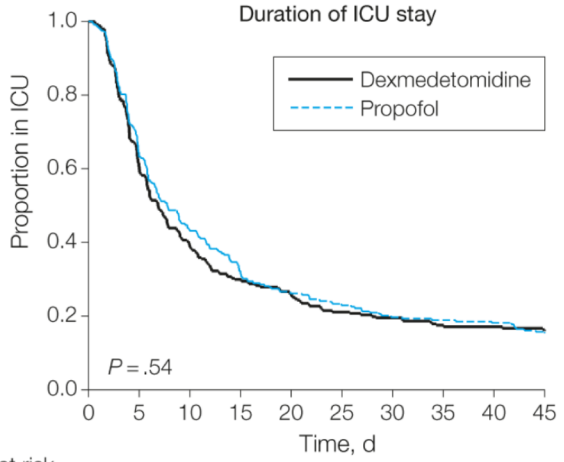
Dexmedetomidine	249	181	115	93	80	72	69	64	63	60
Midazolam	251	203	129	95	79	68	59	56	53	46

B PRODEX trial



No. of patients at risk

Dexmedetomidine	251	111	70	53	45	42	38	35	35	32
Propofol	247	125	82	58	46	39	36	32	32	27



No. of patients at risk

Dexmedetomidine	251	151	97	75	64	53	49	43	43	39
Propofol	247	159	107	79	65	57	49	47	45	37

Table 2. Details of Study Drug Administered and Sedation Stops

	Dexmedetomidine vs Midazolam Study (MIDEX)			Dexmedetomidine vs Propofol Study (PRODEX)		
	Dexmedetomidine (n = 249)	Midazolam (n = 251)	*P* Value	Dexmedetomidine (n = 251)	Propofol (n = 247)	*P* Value
Study drug treatment, median (IQR)						
Duration of infusion, h[a]	42 (23 to 72)	43 (24 to 92)	.15	42 (22 to 72)	47 (25 to 103)	<.001
Dose of study drug, µg/kg/h or mg/kg/h[a]	0.450 (0.273 to 0.756)	0.062 (0.041 to 0.098)		0.925 (0.673 to 1.170)	1.752 (1.211 to 2.424)	
Patients receiving rescue sedation, No. (%)	109 (43.8)	114 (45.4)	.72	182 (72.5)	159 (64.4)	.05
Total dose of rescue sedation, median (IQR), mg[b]	195 (50 to 440)	120 (60 to 300)	.32	17 (6.0 to 41.0)	14 (5.0 to 28.5)	.02
Patients receiving fentanyl, No.	190	207	.10	194	194	.75
Cumulative dose, median (IQR), mg	1.98 (0.54 to 5.77)	2.15 (0.65 to 7.00)	.69	1.83 (0.80 to 5.53)	2.91 (0.75 to 5.67)	.25
RASS score at baseline	–3 (–4 to –2)	–3 (–4 to –2)	.53	–3 (–4 to –2)	–3 (–4 to 3)	.11
RASS score during study drug	–0.9 (–1.9 to –0.1)	–1.5 (–2.5 to –0.5)	<.001	–1.0 (–1.9 to –0.2)	–1.7 (–2.5 to –0.7)	<.001
Time at target sedation without rescue medication, % (95% CI)[c]	60.7 (55.4 to 66.1)	56.6 (51.2 to 61.9)	.15	64.6 (60.0 to 69.1)	64.7 (59.9 to 69.4)	.97
Total sedation stops scheduled/ contraindicated/indicated, No. (%)[d]	717/116/601 (83.8)	859/156/703 (81.8)	.32	658/167/491 (74.6)	888/189/699 (78.7)	.07
Sedation stop performed, No. (%)[e]	539 (89.7)	656 (93.3)	.02	437 (89.0)	630 (90.1)	.56
Duration of sedation stop, median (IQR), h[b]	2.4 (1.0 to 6.3)	3.8 (1.5 to 8.4)	.15	1.3 (0.7 to 3.4)	1.0 (0.4 to 3.3)	.07
Spontaneous breathing trial attempted, No. (%)[f]	317 (58.8)	306 (46.6)	<.001	257 (58.8)	324 (51.4)	.02
Contraindications to performing sedation stop, No. (%)[g]						
Severe oxygenation problems	26 (3.6)	40 (4.7)	.38	57 (8.7)	100 (11.3)	.11
Severe cardiovascular instability	21 (2.9)	20 (2.3)	.53	38 (5.8)	28 (3.2)	.02
Need for continuous or deep sedation	56 (7.8)	61 (7.1)	.63	74 (11.2)	69 (7.8)	.02
Previous sedation stop ongoing	30 (4.2)	45 (5.2)	.34	11 (1.7)	14 (1.6)	>.99
Reasons sedation stop not done, No. (%)						
Other clinical indication	29 (4.0)	26 (3.0)	.28	36 (5.5)	44 (5.0)	.65
Procedure/surgery	14 (2.0)	18 (2.1)	.86	15 (2.3)	17 (1.9)	.72
Logistic reason	18 (2.5)	3 (0.3)	<.001	3 (0.5)	8 (0.9)	.37

Table 3. Patients' Arousability, Ability to Communicate Pain, and Ability to Cooperate With Nursing Care

	Adjusted Mean Estimate (95% CI)			
	Dexmedetomidine	Preferred Usual Care	*P* Value[a]	Estimate of Difference (95% CI)
Dexmedetomidine vs midazolam (MIDEX)	(n = 249)	(n = 251)		
Total VAS score[b]	49.7 (45.5 to 53.8)	30.0 (25.9 to 34.1)	<.001	19.7 (15.2 to 24.2)
Can the patient communicate pain?	46.3 (41.7 to 50.9)	24.2 (19.7 to 28.8)	<.001	22.1 (17.1 to 27.1)
How arousable is the patient?	58.2 (53.7 to 62.6)	40.7 (36.3 to 45.1)	<.001	17.5 (12.7 to 22.3)
How cooperative is the patient?	44.8 (40.3 to 49.2)	25.1 (20.8 to 29.5)	<.001	19.7 (14.8 to 24.5)
Dexmedetomidine vs propofol (PRODEX)	(n = 251)	(n = 247)		
Total VAS score[b]	51.3 (46.9 to 55.7)	40.1 (35.7 to 44.6)	<.001	11.2 (6.4 to 15.9)
Can the patient communicate pain?	49.3 (44.5 to 54.2)	35.4 (30.5 to 40.4)	<.001	13.9 (8.7 to 19.1)
How arousable is the patient?	59.1 (54.7 to 63.4)	47.8 (43.4 to 52.3)	<.001	11.2 (6.5 to 16.0)
How cooperative is the patient?	47.2 (42.3 to 52.2)	38.0 (33.0 to 43.0)	<.001	9.2 (3.9 to 14.5)

Abbreviation: VAS, visual analogue scale.
[a] Analysis of covariance with effects for treatment, country, and baseline values.
[b] A higher score represents a better outcome.